Proceedings of the 2012 IEEE 12th International Conference on Bioinformatics & Bioengineering (BIBE), Larnaca, Cyprus, 11-13 November 2012

What are the symbols of Alzheimer? A Permutation Entropy based symbolic analysis for the detection of early changes of the electroencephalographic complexity due to mild Alzheimer

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Abstract— **Alzheimer's disease (AD) is the most common type of dementia, greatly affecting cognitive functioning and independent living of elderly population. The lack of an available drug therapy that could prevent disease progression shifted the research interest towards the early detection of the neurodegeneration symptoms that affect the mature brain and impair the interaction between brain regions, thus partially causing functional disconnection. The notion of electroencephalographic complexity is a valid and reliable method of quantifying the degree of isolation of brain regions due to AD pathology. Recently permutation entropy, which is a methodology of transforming the signal data into symbolic sequences and then computing the frequency distribution of symbolic patterns, gained great attention and was applied in seizure detection and computation of consciousness. The current study aims to investigate whether this complexity marker would be suitable to be applied in dementia research towards the quantification of the degree of cognitive deterioration due to disconnection of brain regions. The promising results indicate that permutation entropy on posterior regions (parieto-occipital areas) abnormally increases during mild dementia and is negatively correlated with the level of cognitive dysfunction, as estimated by the Mini Mental State Examination. Therefore, it may be a fast, accurate and simple tool for screening elderly population prone in Alzheimer.**

Index Terms—**Alzheimer, Electroencephalography, Permutation Entropy, Resting State, Symbolic Analysis**

I. Introduction

During the last decades, the substantial improvement of life quality and healthcare services led to an important expansion of life expectancy, increasing thus the portion of elderly people who suffer from several chronic diseases. Among the chronic diseases affecting senior citizens, dementia is a common one, posing a substantial burden not only to the patients themselves but also to their relatives and caregivers. The most frequent type of dementia is Alzheimer's (AD). AD's histopathological signature consists of the intraneural creation of neurofibrillary tangles and the extracellural formation of peptide-based plaques [1]. These neurodegeneration phenomena cause deficient cognitive and especially executive functioning, even as early as the preclinical phase of AD [2]. AD also results in a both structural and functional disconnection among distinct brain regions. It often resembles a network breakdown which was shown to be correlated with the degree of cognitive deficits of AD patients [3]. This failure of brain activity integration was verified by several studies and supports the disconnection hypothesis, partially attributed to AD [4]. The decreased cooperation of different neuronal assemblies is reflected on the brain's electrical activity as implied by both synchronization and complexity measures [5], [6]. So, the severity of the neurodegenerative processes has been associated with increased complexity of the electroencephalographic (EEG) signals.

Several methodologies have been proposed for the quantification of the EEG complexity degree. These techniques are mainly derived from nonlinear dynamics and information theory. Among them, the correlation dimension (D2) was frequently used to describe the brain dynamics during sleep, epilepsy, dementia, etc. [7], [8], [9]. It measures the system's dimensional complexity, requiring huge amount of data. Realistic D2 applications assume signal stationarity. Aiming to deal with these problems the notion of Approximate Entropy (ApEn) was introduced [10]. The ApEn could be applied to short EEG segments, while it is noise-resistant. However, it remains time-consuming, while there is no clear insight regarding the selection of the parameter values involved.

Recently, the notion of Permutation Entropy (PE) was introduced [11]. It is conceptually simple, resistant to noise contamination and does not require time consuming

computations, being thus extremely fast. It is based on ordinal time series analysis. During the last decade, it was used mainly in epilepsy research [12] and for the prediction of the anaesthesia depth [13]. To the best of our knowledge, there is no attempt yet to apply the PE on dementia research.

Aiming to propose a simple, yet robust discrimination framework of early neurodegenerative symptoms of AD, we investigated the applicability of symbolic analysis and PE on resting state EEG data collected from elderly participants. Our aim was to verify the previous results of increased EEG complexity on mildly demented patients and to extend those by highlighting the importance of a multi-scale approach for the detection of vulnerable brain regions and frequency bands that were affected by neurodegeneration. The present study aims to exploit the notion of symbolic ordinal analysis in order to introduce a simple, useful and robust tool for neurophysiological screening of elderly population being at the risk of dementia. The proposed EEG analysis framework may serve supplementary to the neuropsychological estimation, providing a direct window to the early pathological brain functioning due to AD.

The remaining of this paper is structured as follows. Details about the experimental procedure, the EEG data acquisition and the permutation entropy analysis are described in the Methodology Section. The results of the statistical analysis are presented in the Result Section and their impact as well as study limitations are discussed in the Discussion Section.

II. METHODOLOGY

A. Participants

The study included 57 elderly participants recruited from day care centers in Thessaloniki, Greece. They were submitted to a detailed neuropsychological examination to acquire a reliable estimation of their cognitive status and to identify patients suffering from mild dementia (MD). Neuroimaging estimation through MRI scan was also applied. The healthy group consisted of 29 participants (21 females), while the MD group consisted of 28 participants (22 females). Both groups were age and gender matched. Inclusion criteria were: age of 58 and older, approval to participate from their personal doctor and signing an informed consent. Exclusion criteria were: drug or substance abuse, recent usage of cholinesterase inhibitors or anti-depressive drugs (less than 3 months), severe neurological disorder due to ischemic attack and severe mobility problems. This study was part of the Long Lasting Memories (LLM) EU FP7 funded program and served as a screening procedure prior to the participants' enrollment. The LLM project proposed the combination of cognitive and physical exercise towards the enhancement of cognitive functioning and independent living [14]. Prior to their participation, the participants were informed about the research procedure and aims. Then, they had the chance to ask for any information regarding the study and signed an informed consent form. The study was approved by the local ethical committee.

B. Neuropsychological Assessment

The neuropsychological examination focused on the reliable detection of cognitive impairment due to mild dementia. Therefore, it employed the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) test. The MMSE is a generic screening tool briefly examining memory, attention and other cognitive functions sensitive to dementia. It is able to detect patients suffering from mild dementia [15]. If combined with the MoCA test [16], the neuropsychological examination's discrimination power is further strengthened since it could differentiate demented elderly from those suffering from Mild Cognitive Impairment (MCI). Participants were also assessed for possible depressive symptoms through the short form of the Geriatric Depression Scale (GDS), which consisted of 15 questions [17]. They were also assessed for several cognitive functions of crucial importance such as verbal memory (California Verbal Learning Task / CVLT) [18], psychomotor speed and executive control function (Trail Making Test Parts A & B / TMT A & TMT B) [19] and working memory through the Digit Span [20]. Another important aspect is the participants' functional ability regarding independent living, which was measured by the Instrumental Activities of Daily Living (IADL) [21]. The participants' life quality was subjectively estimated through the short version of the World Health Organization Quality of Life Instrument (WHOQOL-BREF) in terms of physical, psychological, social and environmental aspects [22].

C. Neurophysiological Data Acquisition & Pre-processing

The neurophysiological data acquisition was performed with a Nihon Kohden JE-207A equipped with active electrodes attached on a cap fitted to the scalp. The device consisted of 57 electrodes recording brain signals, 2 reference electrodes placed on the left and the right mastoids and a ground electrode located at the left frontotemporal borderline. The electrode impendances were approximately 2 KΩs and the sampling rate was at 500 Hz. The participants were instructed to sit in a comfortable armed chair, to close their eyes and to stay calm for four minutes. This resting state data acquisition was part of a longer neurophysiological examination.

The electrodes of each hemisphere were re-referenced according to the activity of the mastoid located on the same hemisphere. The electrodes located on the anterior-posterior midline were re-referenced according to the mean activity of the two reference electrodes. Then, the Independent Component Analysis (ICA) algorithm was applied to recognize artifactual sources. These sources were removed in order to eliminate their contribution to the brain data. Then, visual inspection took place for rejecting short data segments that still were being contaminated with noise. The aforementioned preprocessing steps were performed through the EEGLAB graphic user interface [23].

The final dataset was visually inspected once more and 20 seconds of continuous, high quality, artifact-free data were selected as an input to the PE algorithm. Since many participants felt sleepy during the data acquisition stage,

special attention was paid on the recognition of sleepy states, which were also rejected. Then, the ordinal, symbolic analysis framework was executed for each dataset.

D. Symbolic Analysis

The permutation entropy notion is simple, since it assigns to each data sample a symbol and then it organizes these symbols according to their relative values. Firstly, the embedding dimension parameter *n* has to be introduced. This parameter defines the length of the symbol sequence. For example, if we define the embedding dimension to be n=4, then the symbol sequence has a length of n+1=5, since we have the current symbol and its four previous neighbors. So, the current data sample is denoted as "a", its immediate previous neighbor as "b", etc. Let us regard the following time series: x = (4, 6, 2, 3, 7). So, we have "a"=7, "b"=3, "c"=2, "d"=6 and "e"=4. Thus, we come up with an alphabet that consists of five letters. Then, a specific word is formed by sorting the five symbols into descending order. Regarding our example, the word formed is "adebc" (Fig. 1). Since, the alphabet consists of 5 letters there are 5!=120 available words. Another important parameter of the PE algorithm is that of time lag *r*. The r parameter defines the alphabet's sampling frequency (Fig. 2). For example, if we set r=1 then we consider consecutive data points, whereas in case of r=2 we regard the current data point (x_n="a") as symbol "a", we omit the previous one and we regard as symbol "b" the x_{n-2} data point. Therefore, when we would like to detect high frequency content we should decrease the value of the r parameter.

E. Proposed Analysis Framework

The proposed analysis adopts a multi-scale approach aiming to detect symbolic patterns from both high and low frequency spectrum. This was achieved by computing the permutation entropy with time lag (r value) ranging from 2 to 50 (Fig. 2). The length of symbol sequence was set to 5, while each brain channel segment corresponds to 20 ms (time series length 10000 points). The PE algorithm executed for each channel signal separately and for each time point, assuming there is sufficient number of previous points in order to form the symbol sequence for each time lag. Therefore, in case of r=2, the first sample that could be processed is the N-(4×r+1), which is the 9th signal. For each time series, we obtain the relative frequency p_i of each one of the i=1…120 symbol sequences. It is obvious that the Σp_i =1.0. The permutation entropy notion provides a marker of the signal's complexity by computing the entropy of the symbols' probability appearance through the well-known Shannon's formula:

$$PE=-\sum_{i=1}^{120} p_i \log(p_i) \quad (1)$$

The permutation entropy values are within the range $0 \le PE \le \log(120)=4.7875$. A small value indicates that there are few symbolic sequences with high occurrence, whereas a large value indicates a random (complex) symbolic frequency distribution.

The permutation entropy values were computed for each electrode and for scales ranging from 2…50 with ascending step of 2. Therefore, for each participant we obtained a two-dimensional feature matrix. Each row (i=1…57) corresponds to a single channel location and each column (j=1…25) to a scale level.

Then, a feature selection procedure took place in order to select the most salient features that would be potentially able to discriminate demented patients from the healthy, age-matched elderly. The Euclidean distance among the mean value of the healthy and the demented patients for each feature was computed. The threshold value was set to be greater than 0.0625 and resulted in 10 candidate features. These features were extracted only from the three shortest scales (r=4, 6 and 8) and are presented in Table I.

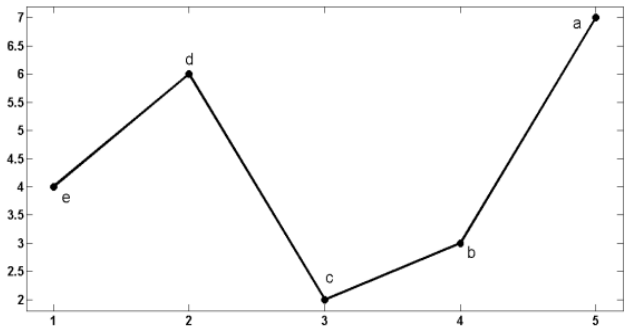

Fig. 1 Visualization of the symbol sequence formation and transformation of the time series data to a symbolic word

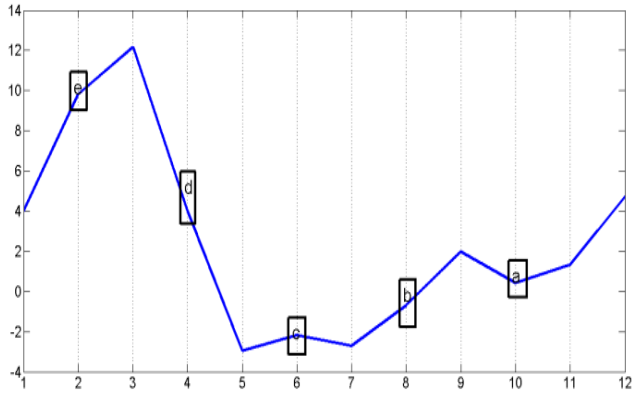

Fig. 2 Visualization of the multi-scale approach and the concept of the time lag parameter when sampling time series data for the symbol sequence formation

Table I. DESCRIPTION OF THE POTENTIAL FEATURES EXTRACTED FROM THE FEATURE SELECTION PROCEDURE

Time Scale (r)	Electrode Locations
r = 4	O2, Pz, POz
r = 6	O2, Pz, CPz, POz
r = 8	P3, O2, Pz

III. RESULTS

The statistical analysis of the permutation entropy values involved independent t-tests. According to the analysis, entropy values for seven out of the ten candidate features differed significantly between the Healthy and the Mild Dementia participants, with the MD group showing

significantly higher entropy values than the Healthy group, as depicted in Table II.

Additionally, a stepwise regression model was employed in order to investigate whether MMSE scores could be predicted from the entropy values in any of the aforementioned PE features. The regression model showed that MMSE scores could be best predicted by the entropy in the right occipital electrode (time lag r=6), β= -14.464, t(46) = 2.799, p = .007. This entropy feature could also predict a significant proportion of the variance in MMSE scores, R^2 = .125, F(1, 55) = 7.837, p = .007.

Table II STATISTICAL ANALYSIS OF THE POTENTIAL PE FEATURES. THE ANALYSIS INVOLVED T-TEST WITH BONFERRONI CORRECTION (α=0.01)

Feature Name	Group	Mean (SD)	t value (df = 55)	Significance
P3 (r = 8)	Healthy	1.95 (0.11)	2.240	.029
	MD	2.01 (0.07)		
O2 (r = 4)	Healthy	1.96 (0.10)	2.429	.018
	MD	2.02 (0.07)		
O2 (r = 6)	Healthy	1.96 (0.10)	2.572	.013
	MD	2.02 (0.07)		
O2 (r = 8)	Healthy	1.95 (0.10)	2.552	.014
	MD	2.01 (0.07)		
Pz (r = 6)	Healthy	1.91 (0.13)	2.376	.021
	MD	1.98 (0.09)		
Pz (r = 8)	Healthy	1.91 (0.11)	2.442	.018
	MD	1.98 (0.09)		
CPz (r= 6)	Healthy	1.94 (0.11)	2.374	.021
	MD	1.99 (0.07)		

Table III CORRELATION ANALYSIS AMONG EACH PE FEATURE WITH THE MINI MENTAL STATE EXAMINATION SCORE

PE FEATURES	Pearson's *r*	Significance Value
	MMSE	
Left parietal (P3, r = 8)	-0.327	0.006
Right occipital (O2, r = 4)	-0.338	0.005
Right occipital (O2, r = 6)	-0.353	0.004
Right occipital (O2, r = 8)	-0.303	0.011
Medial Parietal (Pz, r = 4)	-0.298	0.012
Medial Parietal (Pz, r = 6)	-0.321	0.007
Medial Parietal (Pz, r = 8)	-0.272	0.020
Medial Centro-parietal (CPz, r = 6)	-0.283	0.016
Medial Parieto-occipital (POz, r = 4)	-0.257	0.027
Medial Parieto-occipital (POz, r = 6)	-0.270	0.021

Finally, correlation analysis was performed among each PE feature and the MMSE score. The Pearson's *r* (first row) and the significance (second raw) values are depicted in Table III.

IV. DISCUSSION

The current study investigated the feasibility of employing the notion of the PE towards the detection of the disconnection effects due to AD. This complexity measure was previously used in seizure detection [12] and in quantifying the consciousness level during anaesthesia [13]. These studies demonstrated the robustness of the PE, as well as its easiness in implementation instead of using time-consuming computations. Moreover, symbolic analysis results in a noise resistant methodology, since it is minimally affected by noise fluctuations [11]. The time lag parameter provides the feasibility to adjust the length of symbol sequence. Therefore, permutation entropy could be used for studying dynamical signal patterns of varying frequency content. The attractive properties of the ordinal symbolic analysis motivated us to propose for the first time, to the best of our knowledge, the notion of PE to be used in dementia research. Its simplicity, combined with the robustness demonstrated in other research fields, prompted our hypothesis that it could be an ideal tool for the efficient tracking of dynamic nonlinear brain functioning.

The proposed study verified the previously reported results of increased complexity due to dementia [24], [25]. This finding is attributed to the disconnection among distant brain regions due to AD neuropathology [4]. Each brain area operates in isolation due to mild dementia, resulting thus in increased complexity (less predictability) and impaired cognitive functioning [25]. However, several scientific questions arise regarding the linkage of increased complexity and brain disconnection. Previous studies computed the signal's complexity without considering the issue of time scale [25]. So, their computations considered the whole EEG signal without the feasibility of investigating frequency-varying and frequency-specific patterns. Despite the promising results, a deeper understanding of how AD pathophysiology affects the rhythmic EEG activity is needed. The multiscale approach of the PE enables the examination of the disconnection effects on each frequency band separately. Therefore, the proposed methodology enables us to correlate neurodegenerative phenomena with specific encephalographic rhythms being responsible for a particular brain function. According to the study results, posterior brain regions seem to be more vulnerable to abnormally increased EEG complexity [26]. AD is known to mainly affect areas within the temporal lobe and the hippocampus. However, recent functional, metabolic and neuroimaging findings demonstrated that during early stages of the disease, the parietal cortex is also affected [26]. Our results support this hypothesis since the findings are focused especially on the parietal (medial and left) and on the right occipital cortex.

Another interesting issue is that the statistically significant results were derived from short time lags (r =4, 6, 8). These values correspond to the high frequency rhythmic activity (high gamma, low gamma and beta rhythm respectively). So, it is of crucial importance to understand why the increased complexity is mainly attributed to the fast oscillatory activity. Since the increased complexity is regarded to be due to impaired disconnection, the most probable reason for affecting the

gamma and beta bands is their coordinative role in sensory processing, attention, memory and synaptic plasticity [27], [28]. There is concrete evidence that high frequency oscillatory activity moderates the cooperation among distant brain regions needed for elaborate cognitive functioning. Moreover, reduction of beta oscillations due to EEG slowing is among the earlier neurophysiological symptoms of AD [27].

The proposed study introduced a reliable and robust methodology for the quantification of AD-related neurodegenerative symptoms. However, these initial efforts need to be extended prior to their application in daily screening. Therefore, validation of the method's efficacy with a larger sample (>50 participants per group) is needed. Future work should also include individuals with Mild Cognitive Impairment (MCI). Elderly suffering from MCI face memory impairment of an intermediate degree in comparison with healthy elderly, but they maintain their abilities of independent living and do not fulfill the dementia criteria. Applying the proposed analysis framework towards the early detection of abnormal neurophysiological patterns during this stage may provide a valuable tool for identifying those with increased risk of transition to dementia. The identification of these patients is of crucial importance, since the appropriate intense cognitive and physical training may significantly delay dementia onset. Therefore, we plan to include the proposed analysis to the default screening procedures performed by the Greek Association of Alzheimer's Disease and Related Disorders.

V. CONCLUSION

Concluding, the present study proposes an easy–to-implement, fast and reliable marker of quantifying neurodegenerative symptoms through symbolic analysis and brain complexity. Except from the robust discrimination of the neurophysiological signs of AD neurodegeneration, the method demonstrated the ability to relate these markers to general cognitive decline as measured by the MMSE. So, it may be used as an index of quantifying the disease severity and may have an important role in dementia screening as supplementary to and more objective from neuropsychological examination.

ACKNOWLEDGMENT

This work was granted by the USEFIL ICT FP7 EU funded program.

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