Dynamical Nonstationarity Analysis of Resting EEGs in Alzheimer's Disease

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Abstract. The understanding of nonstationarity, from both a dynamical and a statistical point of view, has turned from a constraint on application of a specific type of analysis (e.g. spectral analysis), into a new insight into complex system behavior. The application of nonstationarity detection in an EEG time series plays an important role in the characterization of brain processes and the prediction of brain state and behavior such as seizure prediction. In this study, we report a very significant difference in the mean stationarity duration of an EEG over the frontal and temporal regions of the brain, comparing 22 healthy subjects and 16 patients with mild Alzheimer's disease (AD). The findings help illuminate the interpretation of the EEG's duration of dynamical stationarity and proposes to be useful for distinguishing AD patients from control patients. This study supports the idea of a compensatory activation of the fronto-temporal region of the brain in the early stages of Alzheimer's disease.

Keywords: Alzheimer's disease, EEG, dynamical nonstationarity, nonlinear system analysis.

1 Introduction

1.1 Early Detection of Alzheimer's Disease Using EEG Time Series

With an increase in life expectancy, dementia-related disorders such as Alzheimer's disease (AD), Parkinson's disease (PD) and vascular dementia (VAD) are having an increasing impact on socio-economic issues and affected over 29 million people worldwide in 2005, with over 4 million new cases every year [1]. Alzheimer's disease has in particular been working to understand the underlying causes and early disturbances of the brain functions due to the progressive course of the disease; the pathological findings include disturbances in the acetylcholine system [2] and deposition of amyloid plaques and neurofibril tangles [3]. Indeed, patients suffering from AD who are detected early are more likely to receive appropriate treatment to slow the progression of the disease, thereby reducing the cost of their treatment as well as reducing the healthcare system expense. Several methods are now available to

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help diagnose AD, including cognitive tests [4], neuro-imaging [5, 6], electro-physiological tests [7, 8], and as a final resource, post mortem analysis of amyloidal plaques and neurofibrillary tangle depositions. In light of the advanced age of the average patient suffering from AD, non-invasive and low-cost methods are preferred, hence the recent interest in EEG analysis the clinical evaluation and diagnosis of early-stage AD.

1.2 Quantitative Study of EEG: Linear and Nonlinear Approaches to Stationarity

Previous studies that have applied quantitative analysis of EEGs in patients with AD can be divided into two approaches: linear and nonlinear methods (see [9] for review). The linear method principally based on spectral, temporal, and spectro-temporal analyses have successfully characterized AD patients in terms of a slowing of the EEGs [10] (i.e. increase in delta and theta powers, and decrease in alpha and beta powers). These findings support the theory of brain reconfiguration in AD patients as the disease progresses, and have also been confirmed by connectivity studies [11, 12]. The characterization of the brain as a nonlinear, deterministic system has justified the application of "nonlinear" methods based on both statistical and dynamical methods extracting associated invariants of the EEG time series [13]. Both linear and nonlinear methods have encountered the well accepted "high nonstationarity" of EEGs as a major limitation to their application. However, the nonstationarity of EEG time series, an intrinsic property of brain electrical signals, appears to be an interesting feature for characterizing brain regimes [14] or state transitions [15].

1.3 Dynamical Nonstationarity Analysis

The current investigation of the EEG time series has revealed several closely related properties that are common to complex dynamical systems (i.e. scaling, complexity, and nonstationarity) and fundamental for interpreting brain (micro/macro) states [15-17]. It was demonstrated that EEGs at rest present a long range correlation and a scale-free set of properties within the alpha and beta bands [18], which is thought to be a hallmark of complex systems with plasticity and multi-time scale correlations (i.e. self-organization) [19]. Statistical nonstationarity (i.e. temporal changes in weak stationary properties such as the mean, variance, or power spectrum) is a consequence of the multi-scale spatio-temporal interaction within the brain, whereas the dynamical nonstationarity (i.e. temporal change in the dynamical parameter of the system) might be both a consequence and facilitator of the spatio-temporal complexity of the brain signals. In this study, we investigated the potential for dynamical nonstationarity to be a viable observation point to differentiate the control brain from AD brain signals during the resting state at a defined scale, which is constrained by the sampling frequency (128 Hz), the window size (W = 250 data points), and the decision threshold (CUT) used in this analysis.

This paper is structured as follows. In Section 2, we briefly introduce the dissimilarity measures that were used as indexes to observe the change in dynamical nonstationarity. We propose a method based on clustering and outlier identification in order to detect combinations of dissimilarity (i.e. in the two-dimensional space of

dissimilarity) that represent dynamical change or transitions. In Section 3, we apply the method to the identification of AD patients when compared with control subjects, in a resting state. Finally, the study is concluded with a discussion of possible clinical applications of the new index to the early detection of AD patients. The aim of this paper is to enhance the understanding of dynamical nonstationarity as meaningful feature of the EEG time series; the issue of temporal/spatial scaling in our method is not addressed, although the interpretation and parameter choice (e.g. length of segments) greatly depend on this factor.

2 Materials and Methods

In this section, we describe the algorithm used to detect the point of changing dynamics (i.e. the dynamical nonstationarity point), as well as the settings of the EEGs and a description of the subjects studied.

Phase Space Density Distribution and Global Dynamical Model. To characterize the nonstationarity of a time series, it is necessary to use dissimilarity measures that are able to distinguish different dynamical regimes. Numerous methods have been proposed to detect nonstationarity transitions of a time series [20-22], but only a few have demonstrated good performance against noise and with a low number of data points (< 1,000). In this study, the density distribution of the phase space [23] and the global dynamical model based on distance polynomial coefficients [24] are used as dissimilarity measures. The details of the computation of these two dissimilarities can be found in the Appendix. The dissimilarities will be calculated for two sets of segments of the original time series comparing temporally successive segments, as explained in the following section.

Segmentation and Clustering. Each time series studied was divided into a first set containing segments of 250 data points (~2 sec) and a second set similar to the first one, but consisting of 125 points (50%). The dissimilarity measures were computed for each set of segments and averaged to form a single, contrasting set of values for each measure, corresponding to the variation in the time of the dissimilarity. The two dynamical indexes of dissimilarity were used as two-dimensional, time dependent (i.e. referring to the comparison of two segments at a given time) coordinates to characterize the temporal variation of the dynamical dissimilarity. The dynamical nonstationarity points form a set of points that have dissimilarity values above the average. Then, we clustered the set of points representing the temporal, dynamical dissimilarity using affinity propagation [25], and the set of nonstationarity points were identified by the clusters with a mean distance to other centers above the threshold θ, defined in Eq. 1:

$$\theta = \mu + CUT * \sigma \tag{1}$$

where μ and σ are respectively the mean and the standard deviation over the inter-center distance, and CUT is a parameter used to modulate the threshold. We also verified that the cluster of nonstationarity points satisfied a sufficient distance to the

origin of the dissimilarity space, so that the chosen clusters are outliers and have high dissimilarity values. We demonstrated that for CUT values ranging from 0 to 1.25, the performance of this method against noise was very satisfying [15].

2.1 Subjects

In this study, we used a group of 16 patients with mild Alzheimer's disease (8 men and 8 women, age = 77.6+10.3) and a group of 22 healthy controls (9 men and 13 women, age = 69.5+11.4). The subjects received full cognitive tests, but neuro-physiological information was unavailable for this study.

2.2 Task and EEG Recordings

The EEG time series were digitalized at a sampling frequency of 256 Hz and downsampled to 128 Hz, using 19 leads on a modified Maudsley system (equivalent to the international 10-20 montage) with the reference at the earlobes. The EEGs were recorded for four minutes during a resting condition with various states: awake, drowsy, and alert, with periods of the eyes closed and open. Hence, this recording is representative of a resting state with spontaneous changes in the state of the subject.

2.3 Statistical Analysis

To compare the controls and AD patients, we first examined the effect of the main factor "diagnostic group" and the within-subject factor "channel" using a repeated measure ANOVA. For the post-hoc analysis, we first performed a Kolmogorov-Sinai test to verify the normality of the mean duration of stationarity, followed by a one-way ANOVA with Welch correction for nonequality of variance. Also, the correction for multiple channels using a Bonferroni correction of the p-value is discussed. All statistical analyses were performed using the statistical package for social sciences (SPSS 13.0).

3 Results

The main effect was only found in the "diagnostic group" ($F = 8{,}596$, $df = 1$, $p = 0.006$), although the "channel" factor was nearly significant ($F = 1.839$, $df = 7.585$, $p = 0.074$, Huynh-Feldt correction). No iteration of the "group X channel" effect was found.

Alzheimer's Disease Patients vs. Controls. In this subsection, we present the results found for the parameters $S = 10$, $d = 3$, $tau = 30$, and $W = 250$ data points; similar results were found for S, d and tau in the range of {5,10}, {3.4} and {20,30}. We found that the AD patients had a shorter duration of stationarity over all channels compared with the controls. The topographic plot of the mean duration time over all leads is presented in Fig. 1.

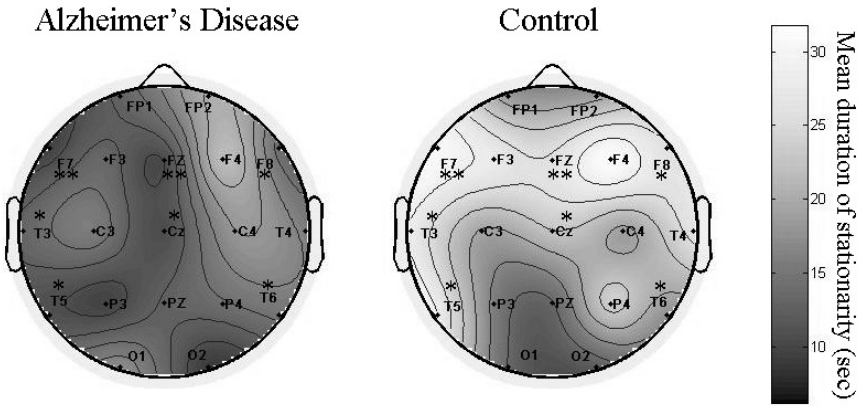

Fig. 1. Topographic plot of the mean duration of stationarity (sec) for Alzheimer's disease patients and control subjects. The leads with significant difference in mean are marked with * ($p < 0.05$) and ** ($p < 0.01$).

We found that the difference in the frontal region was highly significant for leads F7 ($F(1,26.519) = 9.885$, $p = 0.004$) and Fz ($F(1,26.839) = 9.813$, $p = 0.004$), and significant for lead F8 ($F(1,23.435) = 5.948$, $p = 0.023$). The temporal region also exhibited significant differences for leads T3 ($F(1,28.387) = 5.613$, $p = 0.025$) and T5 ($F(1,2.441) = 5.835$, $p = 0.024$) in the left hemisphere, and for leads T6 ($F(1,21.962) = 4.301$, $p = 0.050$) and Cz ($F(1,23.975) = 4.621$, $p = 0.042$) in the right hemisphere. It can be seen that if the Bonferroni corrections were applied, the new p-value would be set to $p = 0.0026$, and none of the differences would be considered significant. The Bonferroni correction in this case might be too conservative and could result in a type II error.

We did not have access to the cognitive tests results, so the correlation between the severity of AD disease and the mean duration of stationarity could not be calculated.

Complexity Results. From our previous study [8], we had found that AD patients had a significantly lower complexity ($p < 0.05$) than the controls for the posterior region of the brain, including the parietal, temporal, and occipital regions. The complexity measures used were the Fractal Dimension (FD), Hjorth Index (HI) and Zero Crossing Interval Distribution (ZCI) [8], and various combinations of those three methods.

4 Discussion

We found the mean duration of dynamical nonstationarity in the EEGs of AD patients significantly shorter than those of the controls in the frontal and temporal regions. The subsequent, significant activation of the two central leads, Fz and Cz, support the existence of a default mode during the resting state [26]. However, since the resting state was somewhat mixed with different states, and also given that other regions

were found to be involved in results, caution should be with this conclusion. The early stages of Alzheimer's disease have been thought to involve the frontal, temporal, and parietal regions. We found that a bilateral region of the brain had a significantly shorter mean duration of stationarity, involving the activation of the region associated with the executive (F8, $p < 0.05$) and memory (bilateral temporal region, $p < 0.05$) functions. This supports the idea of a disruption of normal activities in those regions in the early stages of AD [27, 28]. This result could be interpreted as a form of compensatory activity of the fronto-temporal regions, resulting from a cell-loss-induced reconfiguration of the brain network [28].

The decreased complexity found in AD patients was primarily located in the parietal region and to a smaller extent in the temporal area [8]. In this paper, we do not propose a correlation between the complexity results and the mean duration of stationarity; however, such investigation is a subject for future investigation. We would expect a positive correlation between the short duration of stationarity and high complexity, synonymous with brain activation. Still, it remains unclear how the complexity and nonstationarity are linked. For instance, our previous study on Attention-Deficit and Hyperactivity Disorder (ADHD) supports dynamical nonstationarity being better related to attention change in the brain and a short duration of nonstationarity being more related to a stronger brain activation [29].

In this study, the resolution of the dynamical stationarity was limited by the low sampling frequency of recordings. We will investigate the scaling effect and the influence of the window size, as well as the threshold parameter (CUT), on the mean duration of stationarity for each population in future research. A clear investigation of the relation between the complexity and mean duration of stationarity would be of great benefit to interpret future findings related to those measures.

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Appendix: Dynamical-Based Dissimilarities

Phase space density distribution. Phase space density distribution: the dynamical study of a complex time series often yields a phase space reconstruction, which, under the proper conditions, is able to resituate the geometrically defined, dynamical behavior of the system. The characterization of the phase space by its density distribution [23] is able to extract the dynamical invariants (and to some extent the statistical invariants as well [14]) of a time series and has demonstrated a capacity for detecting slight variations in dynamical parameters of a given deterministic system. Given a time series X, we describe the computation of the dissimilarity measure based on the phase space density distribution and between two segments of X, X1 and X2 as follows:

1. The time series X is normalized into S bins as in equation 1:

$$0 \le s(x(i)) = floor\left(\frac{S*(x(i)-x_{\min})}{x_{\max}-x_{\min}}\right) \le S-1 \tag{2}$$

   Where the floor is a function returning the next lower integer of its input, and xmax and xmin are respectively the maximum and minimum of X.
2. For the two segments X1 and X2, we perform the reconstruction of the phase space using the delay coordinate following Takens'theorem [30]:

$$\begin{aligned} &V_{i,1/2} = \{s(i), S(i+\tau), ..., S(i+(d-1)*\tau\} \\ &i = 1, .., N-(d-1)*\tau \end{aligned} \tag{3}$$

Where Vi,1/2 is a d-dimensional vector for the time i corresponding to the segment X1 or X2. N is the number of points of each segment X1 and X2, and d and τ are the embedding parameters, namely the embedding dimension and the time delay.

3. For each of the reconstructed and partitioned (through binning of X) phase spaces of X1 and X2, we calculate the point density in each unity volume (or space partition). We obtain the spatial density distributions of the reconstructed phase spaces D1 and D1, respectively, of X1 and X2.
   The dynamical dissimilarity is obtained by comparing the two distributions D1 and D2 using a chi-square method:

$$\chi^2(D_1, D_2) = \sum_{l=1}^{B} \frac{(D_1(l) - D_2(l))^2}{D_1(l) + D_2(l)} \tag{4}$$

   Where B is the total number of bins of the distributions D1 and D2.

We estimated the embedding parameters using Kozachenko-Leonenko (K-L) based differential entropy [31] and found that (3,30) and (4,20) for the (d, τ) values were suitable for our EEG data sets. We found that S ranging from 5 to 10 gave a good contrast of dissimilarity, especially against noise [15].

Global dynamical model. As an additional measure of dissimilarity, we used the Euclidian distance between the coefficients of a global dynamical model. This distance between two segments has been consequently used in [14, 24] and demonstrated a capacity for identifying dynamically changing points for appropriately chosen polynomial orders. A time series segment can be reconstructed using a recurrent form:

$$x_{n+1} = f(x_n) \tag{5}$$

Where f is a polynomial function of order p as described in equation 5:

$$f(x_n) = \sum_{i=0}^{p} \alpha_i x_n^i \tag{6}$$

The distance between two segments can be defined as the Euclidian distance between the coefficients of the two segments' model:

$$d = \sum_{i=0}^{p} (\alpha_{i1} - \alpha_{i2})^2 \tag{7}$$

Where αi1 and αi2 are the model coefficients of segment 1 and 2, respectively. We found that polynomial models of an order higher or equal to 6 were sensitive to small changes of dynamical parameters. We chose p = 6 for all analyses.