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Núñez, Pablo (Univ. of Valladolid); Poza, Jesus* (Univ. of Valladolid); Gomez, Carlos (Univ. of Valladolid); Barroso-Garcia, Verónica (Univ. of Valladolid); Ruiz-Gómez, Saúl J. (Biomedical Engineering Group, Univ. of Valladolid); Maturana-Candelas, Aarón (Univ. of Valladolid); Tola-Arribas, Miguel A. (Dept. of Neurology, Hospital Universitario Río Hortega); Cano, Mónica (Dept. of Clinical Neurophysiology, Hospital Universitario R); Hornero, Roberto (Univ. of Valladolid)

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Wang, Fanxin* (University of Illinois at Urbana-Champaign); Toombs, Nicholas (University of Illinois at Urbana-Champaign); Kesavadas, Thenkurussi (UIUC/CHESC); Ferreira, Placid (University of Illinois at Urbana-Champaign)
Characterization of EEG Resting-state Activity in Alzheimer’s Disease by Means of Recurrence Plot Analyses

Pablo Núñez, Jesús Poza, IEEE Senior Member, Carlos Gómez, IEEE Senior Member, Verónica Barroso-García, Saúl J. Ruiz-Gómez, Aarón Maturana-Candelas, Miguel A. Tola-Arribas, Mónica Cano, Roberto Hornero, IEEE Senior Member

Abstract—The main objective of this study was to characterize EEG resting-state activity in 55 Alzheimer’s disease (AD) patients and 29 healthy controls by means of TREND, a measure based on recurrence quantification analysis. TREND was computed from 60-second recordings of consecutive EEG activity, divided into non-overlapping windows of length 1, 2, 3, 5, 10, 15, 20 and 60 seconds. This measure was computed in the conventional EEG frequency bands (delta, theta, alpha, beta-1, beta-2 and gamma). The parameters delay (τ) and embedding dimension (m) were first optimized for every window size and frequency band under study. These embedding parameters proved to be frequency-dependent. Furthermore, 10 s epochs were set as the minimum length required to avoid spurious results. Statistically significant differences between both groups were found (p < 0.055, Mann-Whitney U-test). The groups showed differences in TREND in the theta (4-8 Hz), beta-1 (13-19 Hz) and beta-2 (19.3-30 Hz) frequency bands. Our results using TREND suggest that AD disrupts resting-state neural dynamics. Furthermore, these findings indicate that AD induces a frequency-dependent pattern of alterations in the non-stationarity levels of resting-state neural activity.

I. INTRODUCTION

Dementia due to Alzheimer’s disease (AD) is a neurodegenerative disease induced by the abnormal accumulation of amyloid-beta and tau proteins [1]. AD provokes a localized reduction in white matter integrity, as well as gray matter atrophy [2]. In contrast, healthy elderly subjects show a more widespread pattern of degeneration [2].

Accumulating evidence indicates that AD modifies neural activity, causing a slowing of oscillatory brain activity, abnormal information processing and alterations in connectivity, leading to the identification of AD as a ‘disconnection syndrome’ [3], [4]. These effects are not always detectable, thus impeding the use of electroencephalographic (EEG) recordings for diagnosis, especially during the early stages, where alterations are more subtle [3], [4], [5].

All these limitations prove the need of new methods of EEG characterization. In this regard, recurrence plots (RPs) are a powerful tool to study the properties of dynamical systems, in fields such as astrophysics, economics, meteorology and neurophysiology [6]. RPs are visualizations of the repetition of states (recurrences) in a dynamical system that require no transformation of the data, and from which a diverse set of measures of complexity can be derived [6], [7]. These include entropy, determinism, laminarity, and TREND. The latter is of particular interest when it comes to AD resting-state recordings, as it provides information on non-stationarity (especially if a drift is present) [6]. Preliminary findings pointed to abnormal levels of non-stationarity in AD [8]. TREND is based on recurrence quantification analysis (RQA), i.e., the quantification of small scale structures in RPs [6].

As RP-derived measures require no transformation of the data, their use could offset the pitfalls of other measures derived from Fourier analyses, which assume stationarity of the data and work more adequately with long datasets [7]. In this paper, we therefore aim to characterize EEG dynamics in AD patients and healthy controls during rest by means of a measure derived from RPs. To this end, the secondary objectives of the study are: (i) to derive optimal RP embedding parameters for the analysis of resting-state EEG; (ii) to determine the effect of epoch size on the stability of TREND; (iii) to evaluate the differences in dynamic neural patterns between groups.

II. MATERIALS

A. Subjects

The study sample was formed by 84 subjects: 55 patients with dementia due to AD and 29 cognitively healthy controls. Patients with dementia due to AD were diagnosed according to the criteria of the National Institute on Aging and Alzheimer’s Association (NIA-AA). The control group was composed of elderly subjects with no history of neurological or psychiatric disorders. Table I shows the socio-demographic and clinical data for each group.
Patients with AD Controls
Number of subjects 55 29
Age (years) (med[IQR]) 81.9[76.75 83.25] 75.8[74.2 77]
Sex (M:F) 23:32 8:21
Education level (A:B) 41:13 9:20
MMSE (med[IQR]) 22[19.5 23] 29[28 30]

where ε is a threshold, Θ(·) is the Heaviside function and ||·|| is a norm (in this case the Euclidean norm). The threshold ε must be carefully selected to avoid effects such as artifacts (too large) or lack of recurrence points (too small) [6]. It has been shown that for EEG data, a rule of thumb for the threshold selection is 0.25 of the standard deviation of the data [9].

### B. TREND

**TREND** is a linear regression coefficient over the recurrence point density $RR_\tau$ and provides information on the non-stationarity of a process [6]:

$$TREND = \frac{\sum_{\tau=1}^{N}(\tau - \bar{N}/2)(RR_\tau - \langle RR_\tau \rangle)}{\sum_{\tau=1}^{N}(\tau - \bar{N}/2)^2},$$

(3)

where

$$RR_\tau = \frac{1}{N-\tau} \sum_{i=1}^{N-\tau} R_{i,i+\tau}.$$  

(4)

The computation of **TREND** excludes the edges of the RP ($N < \bar{N}$) due to not having enough recurrence points [6]. In this case $\bar{N}$ was chosen to be $N - 2$ [7]. If **TREND** assumes values different from zero it means recurrent points are heterogeneously distributed across the RP [10]. Its interpretation, however, is not trivial and can yield ambiguous results [6]. $RR_\tau$ can be seen as a generalized auto-correlation function [6]. Since **TREND** is a linear regression coefficient, if the recurrence point density $RR_\tau$ experiments a sharp decrease near the diagonal of the RP and then stays at similar levels throughout it, the **TREND** could be of a lower absolute value than that of an RP with a more gradual decrease of $RR_\tau$. Thus, we have interpreted the results as differences in the dynamical properties of the system between groups.

### C. Stability of the measure

Since the RQA analysis was based on a sliding window and **TREND** is highly dependent on its size [6], the effect of epoch length on the measure must be assessed. The epoch lengths used in the study were: 1, 2, 3, 5, 10, 15, 20 and 60 s. In order to prevent unreliable results in lower frequency bands due to an insufficient number of EEG cycles in the epoch, we computed the grand-average **TREND** values of all subjects and selected the smallest window size with no statistically significant differences with the next greater one ($p < 0.05$, Wilcoxon test, FDR corrected).

### D. Protocol

The protocol of the study was as follows: firstly, the embedding parameters delay ($\tau$) and dimension ($m$) were optimized by means of the widely used mutual information function and the nearest neighbors algorithm [6], respectively, for each subject, epoch size and frequency band under study: delta ($\delta$, 1-4 Hz), theta ($\theta$, 4-8 Hz), alpha ($\alpha$, 8-13 Hz), beta-1 ($\beta_1$, 13-19 Hz), beta-2 ($\beta_2$, 19-30 Hz) and gamma ($\gamma$, 30-70 Hz). Afterwards, for each frequency band, the median values were selected. The delay ($\tau$) must be optimized first,
as the nearest neighbors algorithm has a dependence on its value [11]. In a second step, TREND was computed by means of a sliding window approach, in the conventional frequency bands. The whole 60 seconds of activity were filtered before segmentation. Thirdly, the stability of TREND was assessed. Finally, statistical comparisons between controls and AD patients were performed to evaluate possible differences in the level of non-stationarity. After an exploratory analysis to evaluate the distribution of the TREND values by means of the Shapiro-Wilk (normality) and Levene (homoscedasticity) tests, it was determined that the results did not meet parametric test conditions. Thus, Mann-Whitney U-tests were used to detect statistical differences between grand-average values for each frequency band.

IV. RESULTS

A. Selection of embedding parameters

Table II shows the selected $\tau$ values in milliseconds, while Table III shows the selected embedding dimensions $m$. In the case of $m$, the most common value for all epoch sizes was selected for the subsequent computations ($m = 4$ in every frequency band), so that the values for every epoch size were comparable.

B. Stability of the measure

Fig. 1 shows the grand-average TREND values for every frequency band and epoch size. The minimum epoch size that showed no statistically significant differences with the next greater one ($p < 0.05$, Wilcoxon test, FDR corrected) was 10 s in the delta band and 2 s in the theta band. Thus, we hypothesized that approximately a minimum of between 12 and 25 EEG cycles was required for an adequate characterization of non-stationarity, depending on the frequency band. Hence, we selected an epoch size of 10 seconds as the minimum length that fulfilled this requisite, while allowing the characterization of as many EEG windows as possible. All further tests were performed on the TREND values obtained from 10-second epochs.

C. Statistical analyses

Fig. 2 shows the grand-average TREND values for each frequency band using an epoch size of 10 s. Statistically significant differences between controls and AD patients ($p < 0.05$, Mann-Whitney U-test, FDR corrected) were found in the theta, beta-1 and beta-2 frequency bands.

V. DISCUSSION

In the present study, we assessed the dynamics of resting-state EEG recordings in healthy controls and AD patients by means of an RQA-based measure (TREND). The optimal delay ($\tau$) values decrease in general with the frequency band, which can be explained due to the fact that low frequency bands need a larger delay to avoid the construction of autocorrelated space vectors [11].

We found that a minimum value of between 12 and 25 signal cycles per epoch is needed for reliable estimations of changes in dynamical properties of the system. This could be explained as an effect of measuring spurious correlation effects not due to real recurrences [6], as the epochs are not long enough to accurately represent the evolution of EEG states in the specific frequency band.

Statistically significant TREND differences between controls and AD patients were found in the theta, beta-1 and beta-2 bands. Controls displayed higher TREND values in beta-1 and beta-2, while the opposite occurred in theta. These results suggest that the dynamic properties of EEG resting-state activity differ between controls and AD patients. Several studies have observed dissociated behavior in AD EEG variability in high and low frequency bands, which is in line with our results [4]. The opposite behavior found in the theta band compared to higher frequencies may be related to the decrease in alpha band power, which has been widely reported in AD [1]. This slowing of EEG activity shifts peak power to the theta band, which has been found to be correlated with global brain atrophy or volumetric changes of sub-cortical white matter [1]. Previously, a relationship between relative power and EEG non-stationarity has been found, further supporting this hypothesis [12].

This study has two main limitations: firstly, the characterization of EEG dynamic properties can be approached from different points of view. There are a wide variety of methods to quantify them, many of which are based on the time-frequency representations of the signal that should be used and compared. Secondly, a third group of mild cognitive impairment patients should be included in order to assess alterations of EEG dynamics in the prodromal AD stage.

VI. CONCLUSIONS

This research applied an RQA-based measure to characterize the dynamics of EEG resting-state recordings in AD and healthy aging. We have proved the viability of TREND as a measure of EEG recurrences and showed that epoch length is an important parameter to determine when
Fig. 1. TREND violin plots for each frequency band. Transparent plots represent epoch sizes that showed statistically significant differences with the next greater one ($p < 0.05$, Wilcoxon test, FDR corrected for the number of epoch sizes).

Fig. 2. Violin plots depicting grand-average median TREND values in each frequency band and for each group (controls and AD patients). Statistically significant between-group differences are marked with rectangles ($p < 0.05$, Mann-Whitney $U$-test, FDR corrected for the number of frequency bands).

performing a sliding window analysis. Moreover, TREND is RQA-based, which means it is not affected by Fourier analysis limitations. We also showed that the embedding parameters $\tau$ and $m$ should be optimized for every frequency band separately, as there is a dependency, especially for the delay ($\tau$). Finally, the statistically significant differences in TREND found between controls and AD patients suggest that the neurodegenerative processes in AD induce a frequency-dependent pattern of alterations on the dynamic properties of resting-state neural activity.

REFERENCES


