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Abstract: (1) **Background**: Critical states present scale-free dynamics, optimizing neuronal complexity. We explored electroencephalogram (EEG) criticality in amnesic Mild Cognitive Impairment (aMCI) patients with clinical improvement in working memory, verbal memory, verbal fluency and overall executive functions after the completion of a 6-month prospective memory training. (2) **Methods**: We compared "before" and "after" stationary resting-state EEG records of right-handed MCI patients (n = 17; 11 females), using the method of critical fluctuations and Haar wavelet analysis. (3) **Results**: Significant criticality enhancement was present in frontotemporal electrodes [mean dif: 0.10; Z = 7, p = .019] and isolated electrodes T6 [mean dif: 0.204; t (10) = -2.3, p = .044] and F4 [mean dif: 0.0194; t (10) = - 2.82; p = .018]. (4) **Conclusions**: EEG criticality agreed with clinical improvement, consisting a possible monitoring biomarker in MCI and Alzheimer's disease. Further evaluation is needed in patients under cognitive training or even drug-modifying therapies.

Keywords: EEG; criticality; Alzheimer's; mild cognitive impairment; cognitive training; disease monitoring; biomarker

1. Introduction

Cognitive decline is a central phenotypic manifestation of dementia. Alzheimer's disease (AD) remains one of the most common neurodegenerative diseases and a leading cause of dementia worldwide [1]. Because of its commonly slow progression, and since the diagnosis is mostly clinical, the time between symptom onset and diagnosis often remains long [2]. The impact on the affected individuals and their families, as well as the socioeconomic burden of the disease demand for earlier identification of the disease, i.e., during the stage of Mild Cognitive Impairment (MCI) [3], when cognitive deficits might still be subtle and thus missed by the clinician, if not carefully examined and regularly reassessed. The analysis of the cerebrospinal fluid (CSF) and other imaging modalities like FDG-PET have been studied for early detection of the disease [1]. As the quest for viable disease-modifying therapies (DMTs), i.e., monoclonal antibodies, has gained momentum, there arises a need for reliable, highly reproducible, cheap, fast, easy-to-perform and less invasive methods that could contribute to early diagnosis or even provide additional measures that would facilitate the selection and screening of subjects undergoing cognitive training or cognitive rehabilitation [4].

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Among possible diagnostic modalities and biomarkers, electroencephalography (EEG), a simple, low-cost and non-invasive technique, has already provided robust results. The processing of resting-state EEG signals with various novel methodologies has shown potential in AD diagnosis and assessment of progression [5]. Regarding spectral markers, increased delta and theta activity with a simultaneous decrease in alpha and beta as well as "slowing" and a "disconnection syndrome" have been described [6]. Linear methods have demonstrated dysfunction of cortical connectivity in AD [7], [8].

Adding to previously methodologies, the theory of brain criticality has been examined in AD subjects in the recent years. Criticality is a dynamical state that occurs near the point of dynamic instability where entropy is decreased and scale-free oscillations in various spatiotemporal patterns are observed [9]. Near the critical point, at a transition phase, criticality is demonstrated by high-amplitude fluctuations that slowly decrease along the characteristic in a logarithmic scale “slowing down” [10], leading to long-range temporal correlations. In every scale-free network a power-law distribution is observed.

According to the theory of self-organized criticality (SOC) "neuronal avalanches" are created during a phase transition in the brain, and there is a great communication of neurons through the largest possible number of synapses [11], i.e., connection of brain activity at various levels of organization and an increase in overall neuronal complexity [12]. This is in line with computation models at the “edge of chaos” [13]. Studying functional connectivity and fluctuations of synchronization levels, Stam et al. documented significant reduction of alpha and beta waves in AD patients, despite the maintenance of SOC [14]. Based on previous data supporting dysfunction of neuronal integrity and connectivity, Vysata et al. compared the power-law exponents in patients with moderate to severe disease, noting a reduction of the system for SOqC and highlighting the need for further validation in patients with milder stages of the disease, like MCI [15]. More recent research by Tait et al. and Kulkarni et al. has shown reduction of EEG complexity during the progression of dementia, providing measures of diagnostic accuracy for the detection of AD [2].

After the formulation of the theory of self-organized quasi-criticality (SOqC) [16], evidence of organization of brain dynamics in a quasi-critical manner has been presented, with exponents maintaining a scaling relation indicative of the proximity to criticality, even when external inputs push these networks away from a critical point [17]. Furthermore, since the role of non-linear dynamics in the approach of human cognition studies has been highlighted [18], research suggests that individuals with strong cognition present neural dynamics that are more closely associated with criticality, in comparison to subjects with weaker cognitive abilities [19].

The purpose of this study is to explore the relation between criticality and homeostatic brain plasticity by investigating brain criticality changes in patients with MCI before and after memory training in association with the documented improvement in neuropsychological evaluations.

2. Materials and Methods

2.1. Study Design

EEG recordings of seventeen right-handed subjects (11 females, 6 males; chi square goodness of fit = 1.47, df = 1, p = .225) with clinically diagnosed amnesic Mild Cognitive Impairment (aMCI) according to Petersen criteria [3]were analyzed in our study. Based on evidence of pronounced prospective memory deficits in patients with AD neuropathology even at the stage of MCI, the patients had previously participated in a 6-month single-blind randomized clinical trial (RCT) of Prospective Memory training [20]. Details on inclusion and exclusion criteria are mentioned in the paper by Agogiatou et al. [21]. The RCT had a naturalistic design for the performance of daily and routine tasks based on visual stimuli. The 6-month training consisted of 48 sessions (1 hour per session, 2 sessions per week). After the completion of the intervention patients exhibited significant improvement in neuropsychological assessments of working memory, verbal memory, verbal fluency, and overall executive functions, as shown by the improvement of activities of daily life (ADL), compared to an age-, gender-, and education-matched control group. We used “before” and

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"after" EEGs to measure and compare changes in criticality indices. The RCT was approved by the Scientific and Ethics Committee of "Alzheimer Hellas".

2.2. EEG Recordings – Data Acquisition

We examined resting-state EEG recordings collected via a 21-electrode Nihon Kohden Neurofax J 921A, using the international 10-20 system (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). Where possible the number of electrodes was extended, beyond the basic arrangement of the 10-20 system. The signals were digitized with the Neurofax EEG-12200 Ver. 01-93.

The frequency was set as follows: fs = 500 Hz and the EEG electrode resistance was less than 5 KOhm. Recordings were taken without the use of filters. The protocol for EEG data acquisition included a 10-minute resting state (5 minutes with eyes open and 5 minutes with eyes closed, while seated upright and with no voluntary movements).

All subjects included in the present study had formally agreed to the conduction of an EEG study both at baseline and after the completion of the RCT. It is noted that all EEGs had been examined by two neurologists and all diagrams were normal.

2.3. Data Analysis

2.3.1. Method of Critical Fluctuations:

The method of critical fluctuations (MCF), originally described by Contoyiannis et al., was employed for the analysis of the EEG time-series [22], [23]. MCF is thought to reveal the critical state, as well as to detect a system's distance to criticality [22], [24]. The main points of the analysis are herein presented.

As seen in Figure 1A, only time-series with stationary sections with at least 1*105 points before and after the intervention were considered for analysis. The histogram of Figure 1B depicts the distribution of turning points, marking the area of turning point discontinuation as a possible fixed point (red dashed line). Fixed points are related to neurons' resting states and are thus investigated for a possible operation at or near a critical state. Consequently, the fixed point's laminar region can then be used for fluctuation analysis (Figure 1C). It is noted, that laminar behavior will be detected, if present, without strict determination of the laminar region.

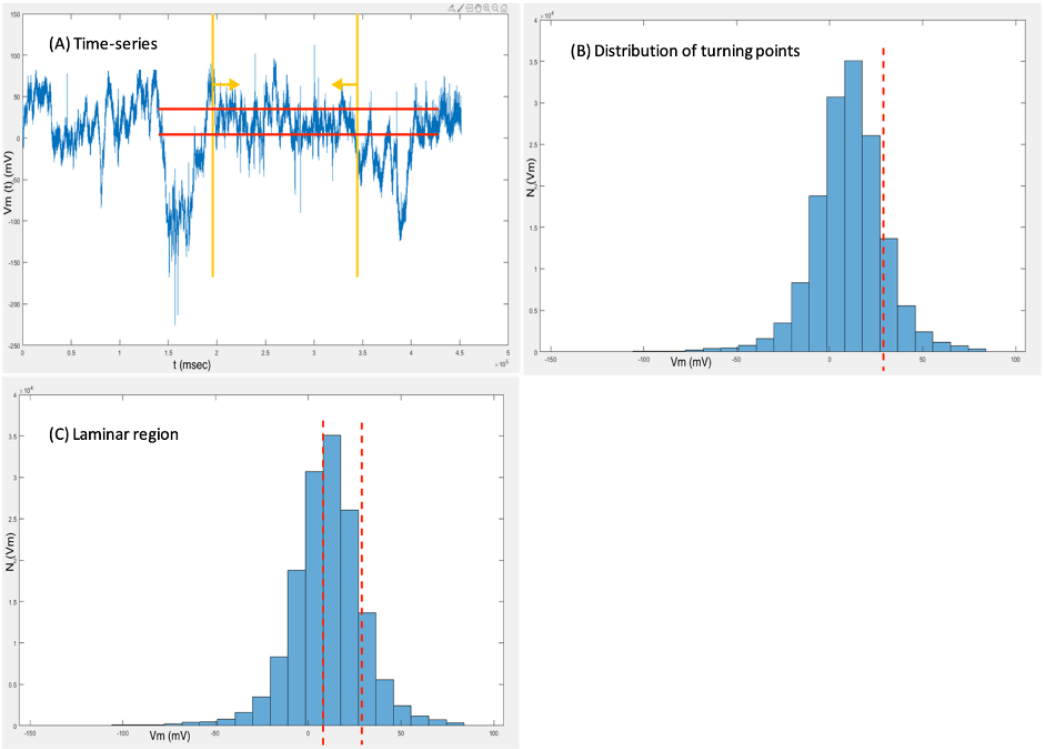

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Figure 1. Estimation of laminar lengths through time-series processing. **(A)** Time-series of an EEG recording. Stationary sections of at least 1*105 points were selected for the analysis. The red lines mark the laminar region. **(B)** Histogram of the same time-series, where the distribution of turning points is depicted; the abrupt discontinuation probably indicates a fixed point. **(C)** The fixed point's neighboring region corresponds to the laminar region used for the analysis.

After estimating the laminar region, it is necessary to estimate the distribution of laminar lengths, i.e., the number of consecutive points in the time series that are within the selected laminar region and consist of intervals with a length from 1 to several tens or hundreds. According to previous studies, laminar lengths follow a power-law distribution when there are intermittent dynamical components in the system [22], [23], a property that can also be quantified at the critical point by creating a criticality map [25], where the potentials at the neighboring points of each fixed point are described by the following function:

$$\phi_{n+1} = \left| \phi_n + u\phi_n^z + \varepsilon_n \right| \bmod 1 \qquad (1)$$

However, these potentials are also reflected in the distribution of laminar lengths given by the following function:

$$\rho(\ell) \sim \ell^{-p} e^{-q\ell} \qquad (2)$$

where parameters p and q describe the long and short range temporal correlations respectively, and are expected to have values p=[1,2] and q≈0 in a critical system [22].

2.3.2. Haar Wavelet Analysis:

The most common causes of noise in the EEG are eye movement artifacts, often leading to wrong conclusions [26]. Noise can affect the discrimination of the power law as well as the point and range of the distribution in which it is identified, leading to miscalculation of the exponent p, and there is no commonly accepted tool that reliably identifies it over a range of scales [27].

The particularity of this work is the analysis based on the Haar wavelet method, which ignores the noise and reveals the power-law distribution and the critical state, if present. Wavelets have been used in this way in the past both to calculate patterns that lead to a power law and to reduce noise [28]. We followed the process introduced by Contoyiannis et al., starting the wavelet processing at a later stage, when the target distribution has already been identified, demonstrating that the information about the existence of the power law lies in the low-scale coefficients that are not affected by noise [27]. Therefore, calculations can be done smoothly even in the presence of noise, bypassing the fitting process. An in-depth review of the methodology is beyond the scope of this study, as it is thoroughly described in the respective paper mentioned above. Therefore, we shall only briefly report the main steps and functions of Haar wavelet analysis.

First, a slightly different approach to the afore-mentioned MCF is introduced. For the extraction of laminar lengths histograms are no longer needed. Figure 2 presents the selection of two points in order to determine the laminar region: Eo (blue line) is a fixed point representing the lower values; EL is a free parameter that signals the end of the laminar region, around the symmetric distribution of EEG values (green line).

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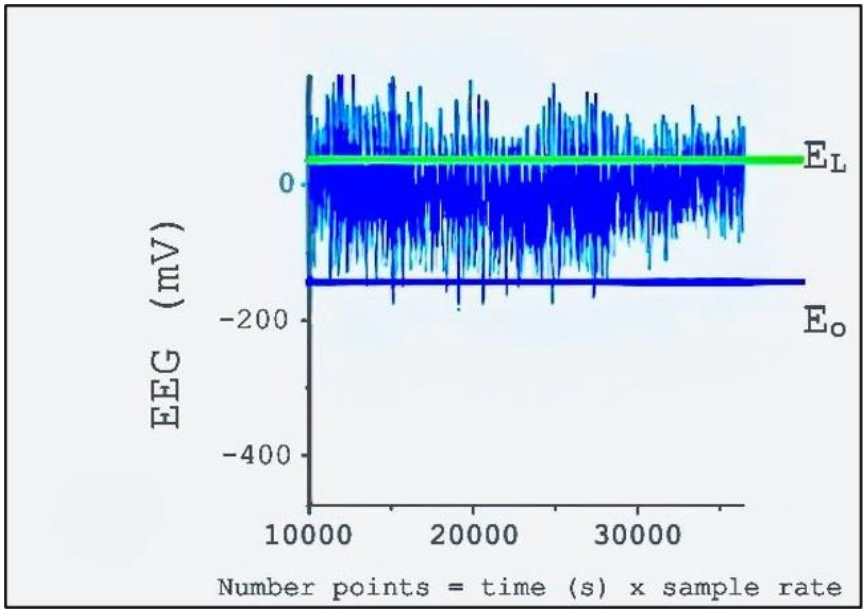

Figure 2. An EEG time-series, from which the laminar lengths can be extracted, using principles of the MCF, but without the need of a histogram. The blue line is a fixed point representing the lower values. The green line is a free parameter that signals the end of the laminar region, around the symmetric distribution of EEG values.

The algorithm on which Haar wavelet analysis is based on the function:

$$\psi_H = \Theta\left(\frac{\Delta}{2} - x\right)\Theta(x-0) - \Theta\left(x - \frac{\Delta}{2}\right)\Theta(\Delta - x) \qquad (3)$$

The calculation is then done with the following functions that determine the following parameters (presented in detail by Contoyiannis et al. [27]

$$\lambda = \frac{\frac{d_{00}}{d_{10}}}{\frac{d_{10}}{d_{20}}} = \frac{d_{00}d_{20}}{d_{10}^2} = \frac{\left(\sum_{i=1}^{\frac{\Delta}{2}} f(i) - \sum_{\frac{\Delta}{2}}^{\Delta} f(i)\right)\left(\sum_{i=1}^{\frac{\Delta}{8}} f(i) - \sum_{\frac{\Delta}{8}}^{\frac{\Delta}{4}} f(i)\right)}{\left(\sum_{i=1}^{\frac{\Delta}{4}} f(i) - \sum_{\frac{\Delta}{4}}^{\frac{\Delta}{2}} f(i)\right)} \qquad (4)$$

$$R = \frac{d_{00}}{d_{10}} = \frac{1}{\sqrt{2}}\left(\sum_{i=1}^{\frac{\Delta}{2}} f(i) - \sum_{\frac{\Delta}{2}}^{\Delta} f(i)\right) / \left(\sum_{i=1}^{\frac{\Delta}{4}} f(i) - \sum_{\frac{\Delta}{4}}^{\frac{\Delta}{2}} f(i)\right) \qquad (5)$$

Finally, the results are quantified. Considering the value $\lambda = 1$ the perfect power law, the distance of λ is calculated using the function:

$$D_\lambda = \sum_{i=1}^{10} (1 - \lambda_i)^2 \qquad (6)$$

Every step of MCF/Haar wavelet analysis was performed twice for the sake of verification. The analyst remained blinded during analysis, with no evidence of the group (before or after) from which each electrode originated.

MATLAB (RRID:SCR_001622) R2019b Update 7 (9.7.0.1471314) was used for the analysis. The codes that we used are given as supplementary material.

2.4. Statistical Analysis

Electrode pairs that presented stationarity both before and after the training were included in the statistical analysis. Descriptive statistics, the Shapiro-Wilk normality test and plot observation were used for data exploration. Means of the λ values before and after prospective memory training were compared for each separate electrode. Mean before and after values of the sum of all electrodes were compared, as well. Additionally, frontotemporal electrodes were isolated and their before and after values were compared. A paired t-test or a Wilcoxon signed-rank test was used, depending on

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the normality of the data. The level of statistical significance was set to 5%. R version 4.1.2 (http://www.R-project.org) was used for the analysis.

3. Results

Our results concerning critical index λ in each separate electrode are presented Table 1. In most electrodes an improvement of mean values after the intervention was noted, although not always statistically significant. In electrode T6, that is placed over the temporo-parieto-occipital (TPO) junction, a statistically significant difference was observed between pre- (M = 0.0827; SD = 0. 138) and post-intervention recordings (M = 0.287; SD = 0.343); t(10) = -2.3, p value = .044. A statistically significant improvement was also presented in the electrode F4, that covers an area of the right frontal lobe, (mdn = 0.0102; IQR = 0.0149 in recordings taken before and mdn = 0.0296; IQR = 0.0252 after the intervention); t(10) = -2.82, p value = .018 (Figure 3A). Values in electrodes PG1, Fp1, P3, P4, Cz and A1, although not statistically significant, showed a lower mean in the λ index after memory training, compared to the initial values (Figure 4).

Pooled λ for all electrodes after prospective memory training was higher (mdn = 0.0331; IQR = 0.0544) than the respective value for electrodes before the intervention (mdn = 0.0226; IQR = 0.0362), but the difference was not significant; Z = 79, p value = .123 (Figure 3B). However, a significant increase was found when only focusing on the comparison of critical index λ from frontotemporal stationary electrodes (before training: mdn = 0.0115; IQR = 0.0134 and after training: mdn = 0.0210; IQR = 0.0261; Z = 7, p value = .019) (Figure 5). The significant increase persisted even when the electrode with the highest increase, T6, was considered a possible outlier and was omitted in a sensitivity analysis (Z = 7, p value = .037).

Table 1. Comparison of the critical index λ before and after the intervention. Pooled values from all patients are presented for each specific stationary electrode. The level of statistical significance was set to 5%.

The critical index λ in stationary electrodes

	Before Prospective Memory training		After Prospective Memory training		
Electrode	λ, mean/median	SD/IQR	λ, mean/median	SD/IQR	p-value
PG1	0,0159	0,0167	0,012	0,00676	0,791*
PG2	0,0237	0,0553	0,139	0,370	0,734†
Fp1	0,00884	0,0139	0,00394	0,0170	0,720*
Fp2	0,0115	0,0164	0,0151	0,0261	0,512†
F3	0,00551	0,01000	0,00565	0,00341	0,069*
Fz	0,0294	0,0468	0,0670	0,00823	0,922*
F4	0,0102	0,0149	0,0296	0,0252	0,018†
F7	0,0188	0,0196	0,021	0,0263	0,814†
F8	0,00969	0,0308	0,0128	0,0139	0,622*
P3	0,0899	0,146	0,0748	0,144	0,806†
P4	0,0548	0,0947	0,0519	0,0533	0,886†
T3	0,00600	0,00921	0,00624	0,00885	1,000*
Cz	0,0211	0,0241	0,0164	0,0163	0,570†
T4	0,0233	0,0278	0,0246	0,0399	0,935*
T5	0,0220	0,0491	0,0416	0,120	0,910*
T6	0,0827	0,138	0,287	0,343	0,044†
O1	0,0363	0,146	0,0366	0,0915	0,413*
O2	0,147	0,260	0,154	0,239	0,906†

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A1	0,0465	0,0652	0,0378	0,0452	0,488†
A2	0,0500	0,0475	0,114	0,337	0,461†
TOTAL	0,0226	0,0362	0,0331	0,0544	0,123*
Frontotemporal	0,0115	0,0134	0,0210	0,0261	0,019*

*: data presented with median (IQR); Wilcoxon signed-rank test. †: data presented with mean (SD); Paired t-test.

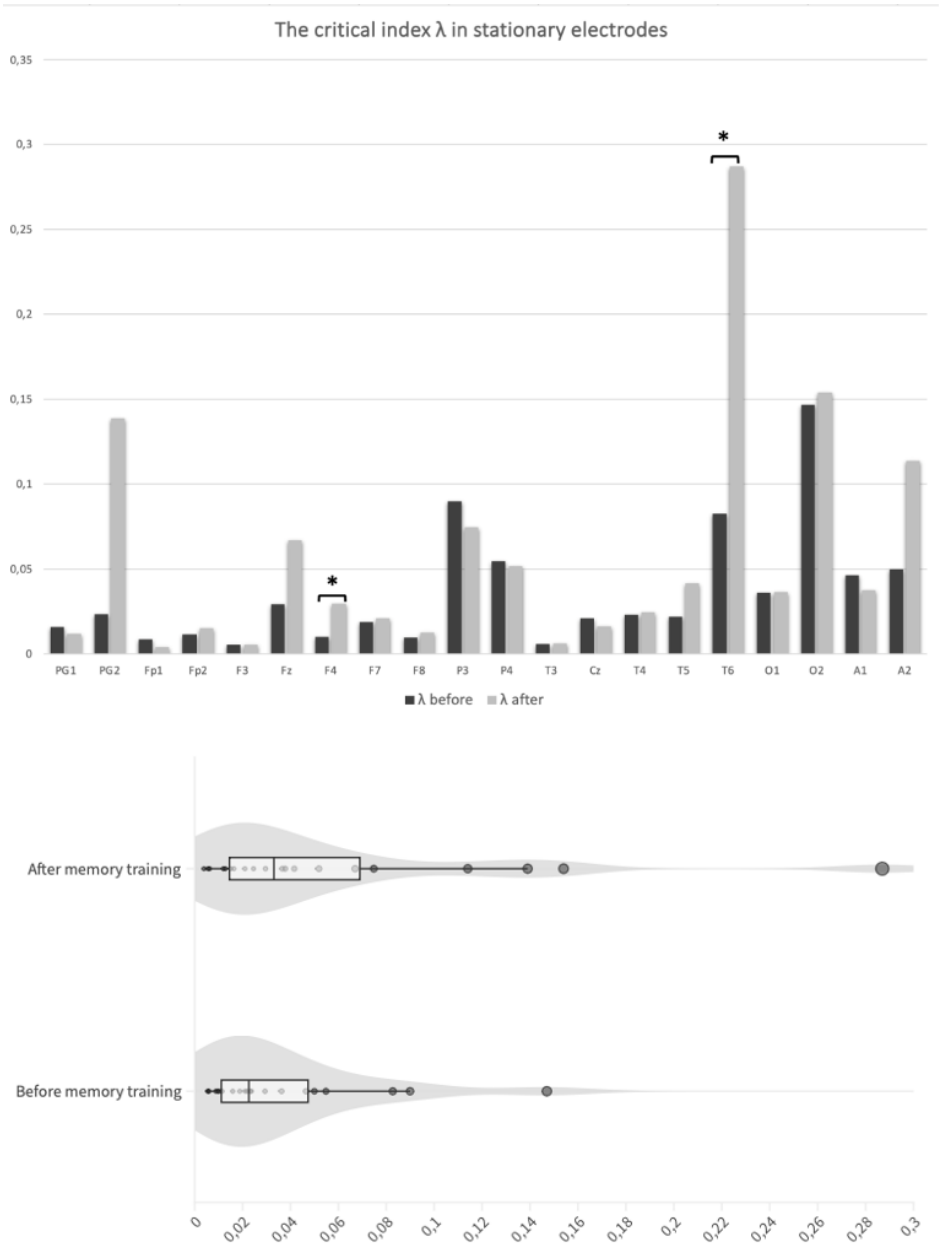

Figure 3. (A) Bar plot presenting the pooled value critical index from all patients for each specific electrode. (B) Pooled critical index λ for all electrodes. After prospective memory training criticality was enhanced in the sum of electrodes (mdn = 0.0331; IQR = 0.0544), compared with the values obtained before the intervention (mdn = 0.0226; IQR = 0.0362). However, no statistical significance is found; Z = 79, *p value* = .123. * indicates statistical significance.

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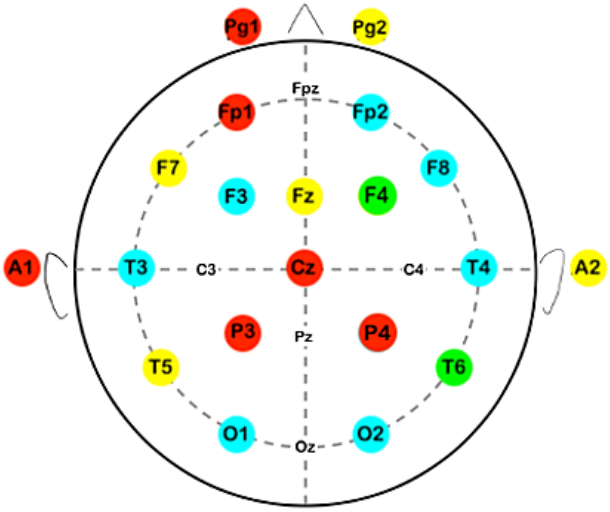

Figure 4. Electrodes with significant improvement after the completion of prospective memory training (F4 and T6), depicted on the 10-20 EEG system. Electrodes are colored according to results of critical index λ after memory training; red: decrease, blue: stability, yellow: increase, green: significant increase.

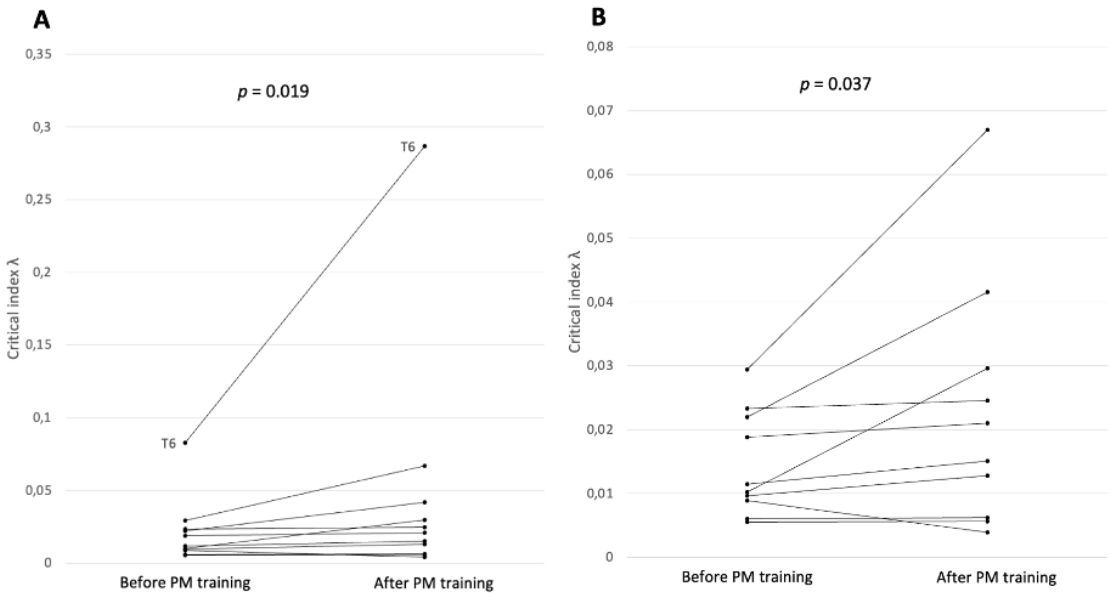

Figure 5. Comparison of the critical index in frontotemporal electrodes before and after memory training. **(A)** The critical index λ was significantly higher after memory training (*p* value= 0.019), with T6 electrode presenting the highest increase. **(B)** A second comparison is presented in which T6 electrode was considered a possible outlier and was omitted. Still, a significant increase is noted among frontotemporal electrodes after memory training (*p* value = .037).

4. Discussion

Our findings support significant enhancement of criticality in frontotemporal electrodes in MCI patients that underwent prospective memory training. Isolated electrode analysis indicated improvement in T6 and F4. It is emphasized that for all patients the traditional EEG examination by two neurologists had shown normal diagrams, both before and after the intervention. Our EEG time-series analysis combined the principles of MCF with Haar wavelet analysis. The limitation of noise

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was overcome, enabling a scale-free approach in the analysis of laminar lengths, since there is no more a need to restrict to small scales that are theoretically invulnerable to noise. We analyzed electrodes with stationary recordings or stationary sections of at least 1*105 points. Contoyiannis et al. examined the methodology in healthy and epileptic subjects, demonstrating absence of a power law distribution in the latter [27]. To our knowledge, this specific methodology was applied for the first time in data deriving from subjects with cognitive decline. Moreover, this is the first study to encompass an EEG criticality analysis in the setting of cognitive training/rehabilitation.

MCI patients that received prospective memory training demonstrated a favorable clinical outcome in working memory, verbal memory, verbal fluency and activities of daily living [21]. These skills have a special neuroanatomic correlation with the topography of the electrodes, in which with criticality enhancement was documented. More specifically, the areas of the brain related to prospective memory, the ability to carry out an action in the future, belong to the frontal, parietal and temporal lobes. The frontal lobe, and specifically the rostral prefrontal cortex and Brodmann area 10, has been associated with event-based prospective memory [29], the temporal lobe has been linked to recognition of stimuli and cues related to the future task [30]. Last, the parietal lobe, and particularly the temporo-parieto-occipital junction (TPO), possibly plays a role in decision making related to time-based prospective memory, by processing and monitoring stimuli related to the performance of a task in the future [31]. Moreover, T6 reflects the neuronal activity of the right temporo-parieto-occipital junction (TPO) of the association cortex (Brodmann areas 37, 39 and 19), a brain region that assembles somatosensory, visual and auditory information and is involved in language, working memory [32], self-processing and recognition of visuo-spatial patterns [33]. F4 reflects the activity of the right premotor cortex and dorsolateral prefrontal cortex (Brodmann areas 9, 8 and 6), that are associated with motor planning working memory [34], speech and verbal description [35]. Therefore, our findings are in accordance with the patients' clinical improvement, expressed through established neuropsychological tests, adding to the internal validity of the methodology.

Interestingly, apart the overall criticality enhancement in frontotemporal regions, significant results from the isolated electrode analysis came from the non-dominant hemispheres of our subjects, since all of them are right-handed. This observation is in line with previously reported findings of rightward dominance and loss of left-hemisphere laterality in right-handed MCI and AD patients, that may suggest activation of right-hemisphere neural resources as a compensatory mechanism [36]. Regarding the rest of the recordings, an improvement was detected in most of the electrodes after the intervention, although not statistically significant. On the contrary, notably but still not significantly lower values were observed in electrodes PG1, Fp1, P3, P4, Cz and A1, which could also be partly explained by compensatory mechanisms and increased recruitment in prefrontal and parietal regions at the initial stages of AD neuropathology, that would justify higher values prior to the intervention [37], [38], [39].

In the context of novel biomarker research in the field of impaired cognition, our results provide evidence for the augmentation of the diagnostic and screening value of the common and easy-to-perform EEG, through the application of brain criticality analysis. Previous work on criticality and the use of EEG has already exhibited promising results. Vysata et al. described a loss of functional connectivity in AD patients, by examining differences from healthy controls regarding power-law exponents on EEG spectrogram, highlighting however the need for future study of this parameter in patients with MCI [15]]. Tait et al. and Kulkarni at al. have shown reduction of EEG complexity during dementia progression [2]. Flores-Sandoval et al. demonstrated a lower EEG spectral power ratio in patients with amyloid-positive amnestic mild cognitive impairment compared with cognitively normal subjects [40]. Trihn et al. evaluated task-induced intra-subject spectral power variability of resting-state EEGs and suggested its use in the early detection of MCI [41]. Our findings are in line with previously conducted research and indicate the possible use of EEG criticality as a screening tool in patients undergoing cognitive training or rehabilitation. We underscore the need for experimental implementation of this parameter in future clinical studies of cognitive training, so that more could be explored regarding critical states and the patients' performance in various tests. Combined with the analysis fluid or neuroimaging biomarkers, criticality could shed light on the

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mechanisms of synaptic brain plasticity or even provide insights about AD theragnostics in patients who will undergo disease-modifying treatments. Furthermore, standardization of the methodology in a wide range of individuals, both healthy and with cognitive impairment, could provide an easy-to-obtain, quantifiable biomarker, that could promote early disease identification and early shaping of treatment strategies in selected patients.

Our study had an explanatory pilot character and its design implies the existence of limitations. Regarding limitations in the analysis, the need for stationarity should be noted, since the methodology could only be performed in electrodes with stationary recordings. Methodologic limitations also include the discrepancy of our results from the theoretically expected values in previous reports of the methodology, highlighting the need for future research in order to standardize expected values. The small number of patients also restrict the external validity of our findings. Moreover, no EEG data were available for MCI patients who abstained from the training, serving as a control group in the RCT. Plus, no comparison was made between MCI patients and healthy individuals.

5. Conclusions

EEG criticality is a promising monitoring biomarker of Alzheimer disease and may have a role in cognitive rehabilitation/training, providing insights of brain plasticity. Furthermore, criticality might be of importance in early disease identification. Future research on large patient cohorts at different disease stages is imperative, with direct comparisons to healthy controls or individuals with other cortical dementias, using standardized methods. Of special interest would be the study of criticality alongside established blood/CSF or neuroimaging biomarkers and in conjunction with amyloid β burden in patients under disease-modifying therapies, that could unlock new paths in Alzheimer disease theragnostics.

Supplementary Materials: MATLAB codes.

Author Contributions: VST; concept framing, data collection, study design, data manipulation/analysis, manuscript drafting/revising. MT; idea conception, concept framing, data collection, study design and manuscript revising. GV; data analysis, manuscript drafting/revising. MS; concept framing, data collection, study design, manuscript drafting. EK; supervision, data manipulation/analysis, manuscript drafting/revising.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The MATLAB codes used for the analysis are publicly available, as a supplementary material.

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Conflicts of Interest: The authors declare no conflicts of interest.

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