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Nonlinear Recurrent Dynamics and Long-Term Nonstationarities in EEG Alpha Cortical Activity: Implications for Choosing Adequate Segment Length in Nonlinear EEG Analyses

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Abstract

Nonlinear analysis of EEG recordings allows detection of characteristics that would probably be neglected by linear methods. This study aimed to determine a suitable epoch length for nonlinear analysis of EEG data based on its recurrence rate in EEG alpha activity (electrodes Fz, Oz, and Pz) from 28 healthy and 64 major depressive disorder subjects. Two nonlinear metrics, Lempel-Ziv complexity and scaling index, were applied in sliding windows of 20 seconds shifted every 1 second and in nonoverlapping windows of 1 minute. In addition, linear spectral analysis was carried out for comparison with the nonlinear results. The analysis with sliding windows showed that the cortical dynamics underlying alpha activity had a recurrence period of around 40 seconds in both groups. In the analysis with nonoverlapping windows, long-term nonstationarities entailed changes over time in the nonlinear dynamics that became significantly different between epochs across time, which was not detected with the linear spectral analysis. Findings suggest that epoch lengths shorter than 40 seconds neglect information in EEG nonlinear studies. In turn, linear analysis did not detect characteristics from long-term nonstationarities in EEG alpha waves of control subjects and patients with major depressive disorder patients. We recommend that application of nonlinear metrics in EEG time series, particularly of alpha activity, should be carried out with epochs around 60 seconds. In addition, this study aimed to demonstrate that long-term nonlinearities are inherent to the cortical brain dynamics regardless of the presence or absence of a mental disorder.

Keywords

EEG recurrence rate, Lempel-Ziv complexity, scaling index, cortical oscillations, EEG nonstationarities, EEG signal processing

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Introduction

The advantages of nonlinear analyses in electroencephalography (EEG) signals have become apparent during the past decades,[1-7] which include the ability to detect certain characteristics of a biological system that from a linear paradigm may be assumed as randomness caused by external disturbances, being reflected as irregularities in their waveforms.[1,8] Rather than actual randomness, some characteristics may be due to a multidimensional deterministic process instead of any stochastic activity.[9,10]

Scaling index (SI) and *Lempel-Ziv complexity* (LZC) are 2 examples of nonlinear approaches. The SI is a measure related to the fractal dimension of a signal that quantifies the self-similarity of its waveform,[11] indicating how rough or smooth the signal is in different time scales according to its fractal properties.[12,13] LZC, on the other hand, has been described in the literature as a method to quantify information directly from a time series associated to its randomness-like level. Both SI and LZC have been employed in several studies aiming to characterize neurological states using EEG signals.[8,14-26] Nevertheless, a key issue in the application of these and other nonlinear measures is their sensitivity to nonstationarities in the time series, which is characterized by variations over time of their statistical properties.[27] In case of EEG signals, nonstationarity episodes could be caused mainly by the sensitivity of dynamical parameters to the different time scales in brain activity,[28,29] most likely reflecting

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dynamical nonstationarity. A complete stationarity in an EEG time series cannot be assured, although it is possible to select epochs where this condition is maximized.

One of the first attempts to establish a suitable epoch length in EEG time series that enhances quasi-stationarity conditions was presented by McEwen and Anderson,[30] indicating that the use of epochs of 2 seconds comprise low nonstationarity. However, Jeong et al[31,32] reported that even an epoch of 6 seconds does not have enough length to show a deterministic structure. Although several authors have developed some parametric and nonparametric methods to detect quasi-stationary epochs in an adaptive fashion,[33-38] these techniques do not allow to obtain epochs of the same duration. Several studies employing SI and LZC are available in the current literature, where authors have assumed durations of epochs to fulfil quasi-stationarity requirements covering values between 1 and 300 seconds.[13,15-24,26,39-47]

In addition to the search of quasi-stationarity conditions, the number of data points also affects the nonlinear deterministic dynamics of these epochs; this is proportional to the sampling rate utilized in the acquisition of the signal, and too short data sets imply errors in the calculation of nonlinear metrics. Although under certain conditions this length should be larger than 100 000 data points according to criterion proposed by Eckmann and Ruelle[48] for generic time series, Gallez and Babloyantz[49] established that data sets larger than 20 000 data points can be suitable for evaluation of Lyapunov exponents in alpha activity, which is a nonlinear measure that quantifies the chaoticity in a time series. Nevertheless, periodical long-term nonstationarity is another aspect that influences a correct selection of the epoch for nonlinear analysis in EEG time series, which has not been taken into account by the rules of quasi-stationarity and number of data points. Periodical long-term nonstationarities are associated to recurrence rate characterized by very slow waves in the brain cortical activity, caused by oscillations in the coupling strength of the neural networks. Tirsch et al[50] reported that the periodicity of these oscillations in the nonlinear behavior of the brain has recurrence times between 50 and 60 seconds. A similar observation was presented in our previous study,[17] in which we evaluated the contribution of nonlinear analysis in patients with major depressive disorder (MDD) to increase the prediction rate of nonresponse to repetitive transcranial magnetic stimulation (rTMS) therapy, compared with prediction evaluated with linear methods only. We found that epoching in minute 1 and minute 2, instead of 10 seconds, allowed to enhance the effects of the nonlinear analysis to realize this prediction.

One of the aims of the present study was to determine an appropriate epoch length for nonlinear analysis in EEG time series based on its recurrence rate, as a methodological contribution for further researches in this field, and its subsequent best use in diagnostic and prognostic uses of EEG in psychiatry. For this study, data comprising 10 minute of eyes closed EEG were recorded, in order to explore the effects of periodic cortical oscillations given the recurrence rate in the brain activity, as well as the effects of the long-term nonstationarities in single EEG time series. The analyses were performed on alpha band activity due to their predominance in the EEG signal[51] and the reported existence of one type of alpha rhythm with nonlinear origin.[29] Given that MDD patients often show deviations in alpha band activity, such as increased posterior alpha and deviating alpha asymmetry,[52] we included both a sample of MDD patients as well as controls, in order to demonstrate that the "optimal" epoch length obtained both applies to controls and patients (ie, to verify if recurrent cortical oscillations and long-term nonstationarities are physiological characteristics of the brain across patients and controls, independent of diagnosis).

Methods

Subjects

EEG data of 28 healthy subjects (average age 34.14 years; SD = 9.72; 13 males) and 64 MDD patients (average age 45.14 years; SD = 14.10; 33 males) were analyzed in this work. The healthy subjects were screened using the Mini International Neuropsychiatric Interview (MINI) structured interview to exclude presence of a psychiatric disorder. MDD patients were screened for major depression or dysthymic disorder by a clinical psychologist using a structured interview (MINI, sections Depressive Episode, Dysthymia, Suicide, Manic Episode, Alcohol Dependence and Abuse and Mixed Anxiety/Depressive Disorder) and were patients awaiting treatment with rTMS therapy. All subjects were asked to refrain from caffeine or nicotine intake for at least 2 hours prior to testing and all patients signed an informed consent form before treatment was initiated.

EEG Data Set Acquisition and Preprocessing

Data were acquired at Research Institute Brainclinics in Nijmegen, the Netherlands, from 26 channels (Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, and O2) in eyes-closed and steady-state condition over a period of 10 minutes (Quikcap; Compumedics NuAmps; 10-20 electrode international system). The acquisition was carried out using a linked ears montage and participants were seated in a sound and light attenuated room that was controlled at an ambient temperature of 22°C. Horizontal eye movements were recorded with electrodes placed 1.5 cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3 mm above the middle of the left eyebrow and 1.5 cm below the middle of the left bottom eyelid. Skin resistance was <5 kohm for all electrodes. The sampling rate of all channels was 500 Hz. A low-pass filter with an attenuation of 40 dB per decade above 100 Hz was employed prior to digitization and a notch filter was applied off-line. Data were offline EOG-corrected using a regression-based technique according to Gratton et al.[53] Subsequently, only the central channels Fz, Oz, and Pz were selected for analyses. Time series were high-pass filtered at 7 Hz and low-pass filtered at 13 Hz (in both cases using zero-phase eighth order Butterworth filters), with the aim to select alpha activity.

Nonlinear and Spectral Analysis

The calculation of the LZC metric was performed employing MATLAB 2015a (The MathWorks, Inc, Natrick, MA) applying a code originally presented by Small[54] and adapted by Fulcher et al,[55] whereas the SI was calculated employing the method presented by Sevcik[56] with an algorithm adapted by Hasselman[57] (for details, see Supplementary Material).

In order to characterize the periodical long-term nonstationarities associated to cortical oscillations, each nonlinear metric was applied in form of sliding windows of 20 seconds and shifted every 1 second, which entailed an overlap of 19 seconds such as performed by Tirsch et al.[50] A numerical result of the nonlinear measure applied was obtained by each iteration, hence a sequence of 579 points was obtained for each of the 3 selected EEG channels (Fz, Oz, and Pz) and for both groups (healthy and MDD subjects). These sequences were smoothed with a zero-phase Butterworth filter of eighth order at cutoff frequency of 0.06 Hz, with the aim to facilitate the detection of the peaks, whose consecutive distances among them represent the recurrence rate of the brain activity. The cutoff frequency of 0.06 Hz was selected based on observation of the spectrum of each sequence. The peaks were detected scanning the sequence from left to right, looking for the compliance of the conditions $x(n) > x(n-1)$ and $x(n) > x(n+1)$, where x represents the sequence and n the scanned time point. Subsequently, the time distances between every couple of consecutive peaks were calculated across all subjects of each group and the values of the median were computed.

A second analysis was carried out to evaluate the effects of the long-term nonstationarities on the nonlinear metrics. In this step, the measures were applied on the selected and preprocessed EEG time series utilizing nonoverlapping windows of 1 minute over a period of 9 minutes. The selection of this length was based on the work presented in Arns et al,[17] where analysis with nonoverlapping windows of 1 minute facilitated the prediction of nonresponders to rTMS. A spectral linear analysis was also carried out via fast Fourier transform in the same way as in the nonlinear analysis, calculating the spectral power by means of trapezoidal integration in the spectrum of every segment in both sliding windows and 1-minute nonoverlapping windows.

Statistical Analysis

The results of the sliding analysis were represented by histograms of the distances between consecutive peaks. Results obtained with 1-minute nonoverlapping windows were processed via an N-way analysis of variance (ANOVA) with 2 within-subject factors, in order to evaluate the effects of channel (3 levels: Fz, Oz, Pz) and time (9 levels: minute 1 to minute 9), as well as the interaction between them employing the function *anovan* within the statistics toolbox of the software MATLAB 2015a. To correct for multiple comparisons, a Bonferroni correction was applied with the function *multcompare* of MATLAB 2015a. This analysis was conducted separately for each group of results, that is, LZC in healthy subjects, SI in healthy subjects, LZC in MDD patients, and SI in MDD patients.

Results

Recurrence Rate in Cortical Oscillatory Activity

The curves in Figure 1 illustrate an example of the sequences obtained from the analysis with sliding windows for a healthy subject and an MDD patient applying the nonlinear metrics and spectral power (indicated as "power" in the plots) to channel Fz. These curves allow to observe the cortical oscillations during a time segment close to 580 seconds.

In Figure 2, the histograms represent the distributions of time differences between consecutive peaks across all subjects per group (controls vs MDD), according to the results obtained with LZC, SI, and power at channel Fz. These results provide insight in the more predominant values of time differences, which vary around 40 seconds. In case of LZC, the averaged time differences and medians (in seconds) were 47.93 ± 15.39, median = 44 for healthy subjects (Figure 2A) and 47.36 ± 14.89, median = 44 for MDD patients (Figure 2B); for SI these values were 46.20 ± 15.05, median = 44 for healthy subjects (Figure 2A) and 48.70 ± 15.60, median = 46 for MDD patients (Figure 2D); for spectral power the values were 47.59 ± 15.16, median = 44 in healthy subjects (Figure 2E) and 48.78 ± 14.81, median = 45 for MDD patients (Figure 2F). Note that the smoothing of the sequences obtained in the sliding analysis (gray curves in Figure 1) may ignore some peaks that could not be detected in the scanning, which is reflected by times around 90 seconds in the histograms. Figures A1-A4 in the supplementary material show the counterparts of the Figure 1 and 2 for channels Pz and Oz, respectively, demonstrating similar results.

Long-Term Nonstationarities

Figure 3A and B illustrates the results of the averaged (mean and standard error) LZC values applying this measure in nonoverlapping continuous segments of 1 minute. An interesting observation is the augmented LZC at channel Fz with regard to the channels Pz and Oz for each group. The N-way ANOVA for the healthy subjects (Figure 3A) showed a channel effect ($p \ll .05$; $df = 2$; $F = 24.37$), and post hoc analysis indicated that the significant differences were in the couples Fz versus Pz and Fz versus Oz, whereas no effects were found for the factor time ($p = .053$; $df = 8$; $F = 1.93$) or for an interaction of channel * time ($p = .999$; $df = 16$; $F = 0.18$). Visually, a nonsignificant trend was observed in the curve of channel Pz, displaying a continuous reduction that started at around 7 minutes. A similar visual trend, albeit with less regular curve, was also observed in

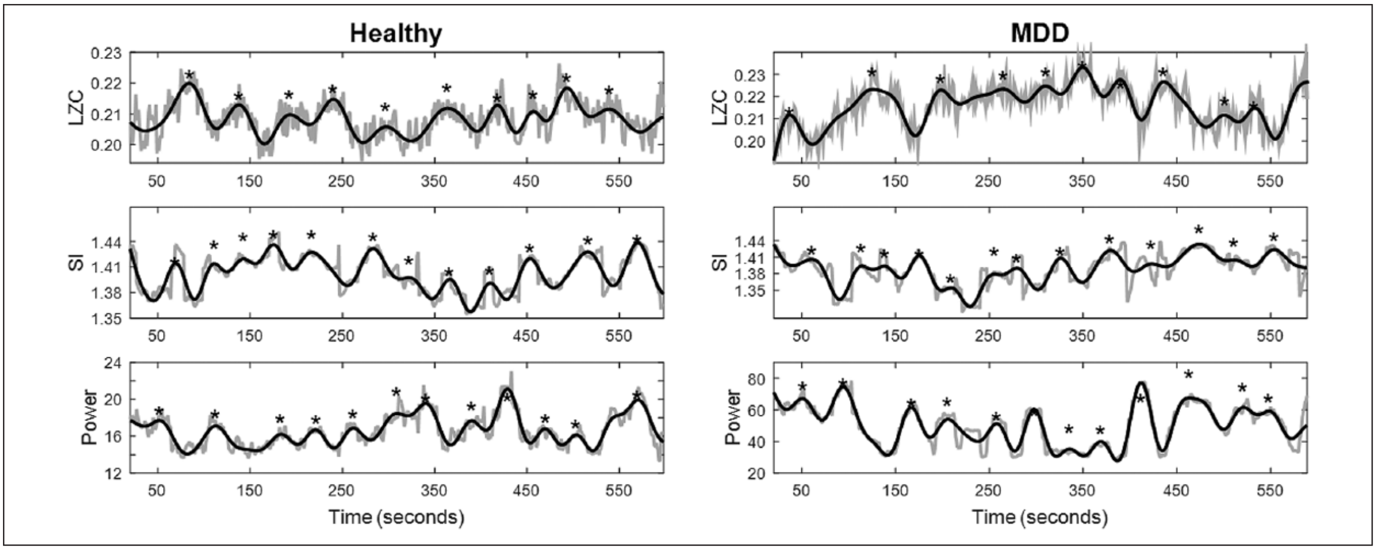

Figure 1. Examples of sequences of nonlinear measures from the analysis with sliding windows for the channel Fz in a healthy subject (A) and a patient with major depressive disorder (MDD) (B). Gray curves, original sequences; black curves, smoothed sequences; asterisks, locations of the peaks detected automatically.

channel Oz. In case of the group of LZC for MDD patients (Figure 3B), the N-way ANOVA analysis found effects in channel ($p \ll .05$; $df = 2$; $F = 27.46$) and time ($p = .005$; $df = 8$; $F = 2.75$), whereas no significant effect was found for the channel * time interaction ($p = .995$; $df = 16$; $F = 0.31$). For the factor channel, post hoc analysis showed significant differences in the 3 couples of channels Fz versus Oz, Fz versus Pz, and Oz versus Pz, whereas the effects of time were represented by significant differences in minute 2 versus minute 9. An interesting nonsignificant trend was the reduction of LZC from minute 1 to minute 2, a subsequent increase from minute 2 to minute 3, continued with the ascending trend up to minute 9. This characteristic was more noticeable in the channels Oz and Pz of the MDD group. All in all, an effect of channel with significant differences between Fz and Oz was established in both groups.

The results for the SI demonstrated an effect of channel ($p = .013$; $df = 2$; $F = 4.4$) and time ($p = .002$; $df = 8$; $F = 3.05$), whereas no effect was detected in the interaction channel * time ($p = .928$; $df = 16$; $F = 0.54$) for the group of healthy subjects (Figure 3C), post hoc analysis demonstrated significant differences in Fz versus Oz, while for the factor time a significant difference was found in minute 1 versus minute 6 and minute 1 versus minute 8. However, in the group of MDD patients (Figure 3D) the N-way ANOVA analysis found effects for both channel ($p \ll .05$; $df = 2$; $F = 16.88$) and time ($p \ll .05$; $df = 8$; $F = 3.94$), but no interaction of channel * time ($p = .990$; $df = 16$; $F = 0.36$). Post hoc analysis demonstrated significant differences for the factor channel with the couples Fz versus Oz and Fz versus Pz, whereas for the factor time these were in minute 2 versus minute 7, minute 2 versus minute 8, and minute 2 versus minute 9. Applying the SI method, in both groups a nonsignificant decreasing trend of the averaged values of the metric was observed. All in all, an effect of channel with significant differences between Fz and Oz was established in both groups.

Note that the absence of effects in the interaction of channel * time for all the 4 groups of analysis indicates that the time effects were independent of channel effects.

Regarding the power spectral analysis (Figure 3E), in the group of healthy subjects an effect of channel was also found ($p < .05$; $df = 2$; $F = 12.28$), whose post hoc analysis detected significant differences Fz versus Pz and Oz versus Pz, but no effects of time ($p = .369$; $df = 8$; $F = 1.09$) or of channel * time ($p = 1$; $df = 16$; $F = 0.08$). A nonsignificant reduction was observed in the 3 channels from minute 1 to minute 5 and afterward an apparent stabilization. In the group of MDD patients (Figure 3F), effects were found only in the factor of channel ($p < .05$; $df = 2$; $F = 15.73$), whose post hoc analysis showed also significant differences in Fz versus Pz and Oz versus Pz. No effects were found in time ($p = .983$; $df = 8$; $F = 0.24$) and in channel * time ($p = 1$; $df = 16$; $F = 0.05$). In both health and MDD subjects, the power of alpha waves in Pz channel was significantly larger in comparison with that in channels Fz and Oz.

Discussion

The present study has been carried out aiming for a better understanding of the long-term brain activity and its quantification, using two nonlinear metrics (LZC and SI) and spectral power to obtain reliable estimates for the optimal epoch length in EEG nonlinear analysis. First, the application of the metrics in the sliding analysis showed oscillatory behavior (ie, a recurrence rate) of the cortical activity with periods around 40 seconds. This finding underlines the evidence of periodic variations in the stability of coupling strength among sources of EEG signals. These periodic variations are associated with the brain's predisposition to transition state between synchronized (low-complex) and desynchronized (high-complex) brain activity,[50]

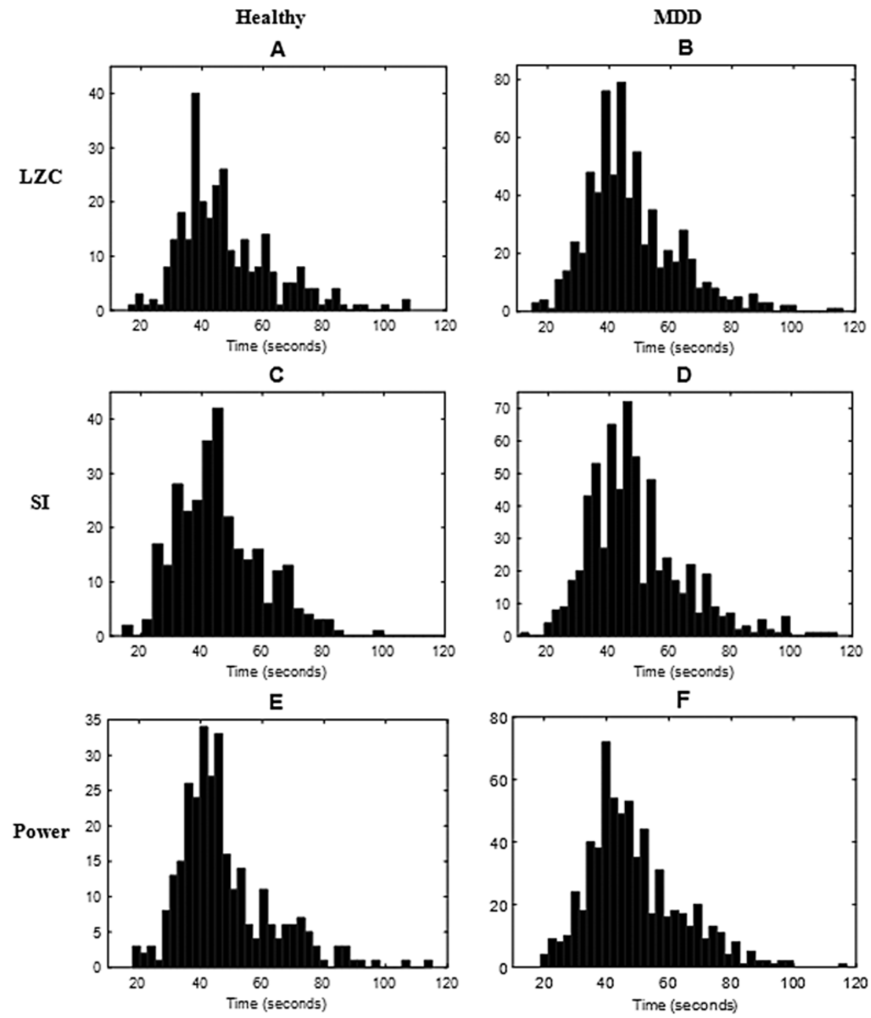

Figure 2. Histograms representing the range of recurrence time of the nonlinear brain cortical activity, detected from the smoothed sequences obtained in the application of the Lempel-Ziv complexity (LZC) and fractal dimension metrics. The histograms were constructed with 60 bins (panels A and C, healthy group; panels B and D, major depressive disorder [MDD] group). SI, scaling index.

in order to control information processing in central and parallel modes.[58] Probably, this recurrence rate is related to the ability to characterize significant neural dynamics in functional magnetic resonance imaging (fMRI) data. In this sense, Liégeois et al[59] reported that time windows between 40 and 60 seconds facilitate the detection of functional and structural neural dynamics; however, further research should be carried out to confirm this association.

Although the 2 nonlinear measures characterize the waveform complexity of a time series in 2 different ways, this periodic oscillatory feature was illustrated with both measures in both healthy subjects and MDD patients (Figure 2A-D). Together with the oscillations observed in the linear spectral analysis (Figure 2E and F), it is evident that choosing too small epochs, such as ranges between 1 and 20 seconds,[16,19-22,39] might neglect valuable information that could be detected by these methods of signal characterization. Second, from the analysis of long-term nonlinearities with LZC (Figure 3A and B), the significant differences between channel Fz with its counterparts at Pz and Oz may be explained by the absence of visual and tactile stimuli. As expected, the larger nonlinear activity recorded from channel Fz with respect to the other 2 channels may be an indication of uninterrupted cognitive actions—or resting state activity—during EEG recording in an eyes-closed resting condition, possibly reflecting thoughts, imagination, memories, and so on. This can be an indication that the location in time of an EEG time series, to be analyzed with nonlinear metrics, should be carefully selected. Figure 3A and B illustrates that nonlinear activity in parietal and occipital lobes reduced as consequence of the absence of visual and tactile stimuli. In this particular case, the application of the linear method entailed synchronization of alpha activity in the parietal and occipital lobes by functional inhibition,[60] as well as their desynchronization in the frontal lobe,[51] so the LZC is inversely proportional to the synchronization of the alpha activity. In case of the MDD group (Figure 3B),

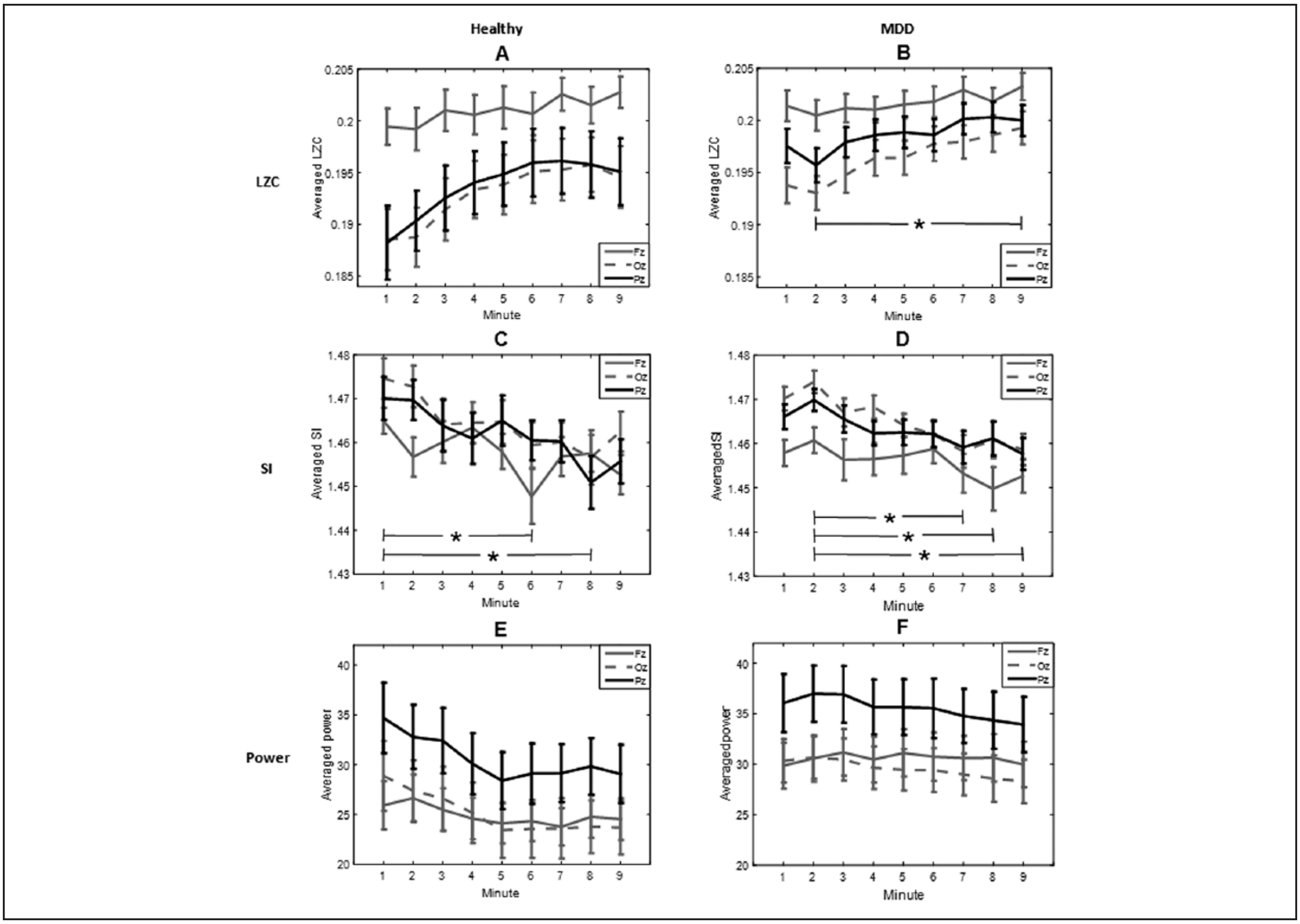

Figure 3. Averaged results of Lempel-Ziv complexity (LZC), scaling index (SI), and spectral power measured every 1 minute in the 2groups of analysis with the information contained in the 3 channels. * Indicates significant time effects ($p < .05$).

significant differences in the measure calculated in minute 9 in comparison with minute 1 was observed in MDD patients, which is thought to reflect long-term nonstationarities. Probably, after multiple minutes of EEG recording vigilance descends entailing arousal later in time. The mentioned synchronization and desynchronization of alpha activity regarding the location of the channels are reflected by increase and decrease of the alpha power in Fz, Pz, and Oz for both groups (Figure 3E and F).

The trends of curves obtained in the calculation of the SI (Figure 3C and D) were anticorrelated with curves obtained with the LZC metric, indicating an increase of complexity linked to a decrease of self-similarity as time augments, resulting in long-term nonstationarities characterized by variations in time of nonlinear dynamics in cortical regions. This assertion is supported by significant differences in minute 1 versus minute 6 and minute 1 versus minute 8 for the healthy group (Figure 3C), and minute 1 versus minute 7, minute 1 versus minute 8, and minute 1 versus minute 9 for the MDD group (Figure 3D). These last observations can be regarded reliable since the rise of random-like activity in the EEG signals implies an increase of complexity affecting the presence of self-similar patterns among large and small scales. Except for the healthy group analyzed with LZC (Figure 3A), significant changes in the nonlinear measures between the first and last time points of the EEG recordings were observed (Figure 3B-D). These could be the consequence of drowsiness building up throughout the measurement or stress that the subjects may present particularly in the initial minutes of the EEG recording, triggering activity in the occipital and parietal lobes together with the frontal lobe. Note that these speculations should be a topic of future investigations. Figure 3E and F deserves a special interest, where it is clearly shown that linear analysis in both groups does not reflect the long-term nonstationarity detected by the nonlinear analysis, such as observed in Figure 3B-D. This fact implies evidently that linear analysis does not detect biomarkers associated to longterm nonstationarities in EEG alpha activity of MDD patients.

In summary, the results of this work allow to infer that future studies carried out for nonlinear analysis of EEG time series, at least for alpha activity, should consider the application of the respective metrics in epochs within the identified recurrence times. For practical purposes, an epoch length of 1 minute is suggested, based on the effects of time detected. Otherwise, it should be in the range between 40 and 60 seconds in order to obtain reliable estimates. As reported by Arns et al,[17] LZC was associated with treatment response to rTMS in an MDD sample, only when using a 1 minute EEG epoch length, whereas that same information was lost when using shorter epoch length. Furthermore, this LZC metric contained data independent of linear measures such as alpha power and alpha peak frequency, demonstrating added value of such measures in biomarker research. The current study collected 10 minutes EEG data to better investigate the true recurrence rate inherent to the data, which confirmed that indeed a 1 minute epoch length seems optimal for nonlinear characterization of EEG time series. Absence of effects of time in spectral analysis for both groups suggests that epoch lengths larger than 40 to 60 seconds are not required for linear analysis. The present work confirms that long-term nonstationarities are inherent to the cortical brain activity regardless presence or absence of mental disorder.

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Author Contributions

AC, MV and MA assisted in setting up the study design and editing the intermediate and final versions of the manuscript, AC conducted all signal processing and data analyses.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary Material

Supplementary material is available for this article online.

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