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ORIGINAL ARTICLE

'Knock down the brain': a nonlinear analysis of electroencephalography to study the effects of sub-concussion in boxers

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Abstract

Background and purpose: Boxing is associated with a high risk of head injuries and increases the likelihood of chronic traumatic encephalopathy. This study explores the effects of sub-concussive impacts on boxers by applying both linear and nonlinear analysis methods to electroencephalogram (EEG) data.

Methods: Twenty-one boxers were selected (mean ± SD, age 28.38 ± 5.5 years; weight 67.55 ± 8.90 kg; years of activity 6.76 ± 5.45; education 14.19 ± 3.08 years) and divided into 'beginner' and 'advanced' groups. The Montreal Cognitive Assessment and the Frontal Assessment Battery were administered; EEG data were collected in both eyes-open (EO) and eyes-closed (EC) conditions during resting states. Analyses of EEG data included normalized power spectral density (nPSD), power law exponent (PLE), detrended fluctuation analysis and multiscale entropy. Statistical analyses were used to compare the groups.

Results: Significant differences in nPSD and PLE were observed between the beginner and advanced boxers, with advanced boxers showing decreased mean nPSD and PLE (nPSD 4–7 Hz, $p = 0.013$; 8–13 Hz, $p = 0.003$; PLE frontal lobe F3 EC, $p = 0.010$). Multiscale entropy analysis indicated increased entropy at lower frequencies and decreased entropy at higher frequencies in advanced boxers (F3 EC, $p = 0.024$; occipital lobe O1 EO, $p = 0.029$; occipital lobe O2 EO, $p = 0.036$). These changes are similar to those seen in Alzheimer's disease.

Conclusion: Nonlinear analysis of EEG data shows potential as a neurophysiological biomarker for detecting the asymptomatic phase of chronic traumatic encephalopathy in boxers. This methodology could help monitor athletes' health and reduce the risk of future neurological injuries in sports.

KEYWORDS
boxing concussion, chronic traumatic encephalopathy, dementia, nonlinear EEG, sub-concussion, traumatic brain injuries

INTRODUCTION

Sports-related head injuries are prevalent across numerous sports [1]. Amongst these, athletes in contact sports such as American football, rugby, boxing, hockey and soccer face a disproportionately high risk of brain damage and pathological disorders related to sports participation [2]. In particular, a study of high school athletes in the United States found that American football had the highest incidence of head injuries [3]. Boxing is also considered as a high-risk sport, with an estimated 17% of former professional boxers showing signs of chronic brain injury due to repeated trauma [4]. Over the last century, growing economic interest in sports has led to increased institutional focus on the safety and public health of athletes. This attention has coincided with a reported increase in brain trauma injuries [5,6]. Annually, over 1.5 million Americans suffer a traumatic brain injury, predominantly classified as a concussion or mild traumatic brain injury [7]. Of particular concern is brain damage caused by single traumatic events in a sports context (sports-related concussions).

In the area of sports-related concussions, repeated head impacts are a major concern for athletes [8–10] and are associated with the development of chronic traumatic encephalopathy (CTE) [11], a complex neurodegenerative disorder widely recognized as one of the major chronic diseases stemming from contact sports and martial arts [12]. The first acknowledgement of CTE dates back to 1928 when Harrison Martland described a syndrome he called 'punch drunk', in which professional boxers exhibited behavioural problems and signs of mental deterioration [13]. Subsequently, the term 'dementia pugilistica' (DP) was introduced by Millspaugh [14] in 1937 to extend the concept to other contexts beyond boxing.

Chronic traumatic encephalopathy encompasses a broad spectrum of neurological disorders, often characterized by cognitive decline, personality changes, behavioural changes, language deficits and motor impairments such as dysarthria, cerebellar ataxia, parkinsonism and hyperreflexia. Cognitive symptoms may include memory loss, attention deficits, slowed information processing, confusion and irritability [15]. Recent studies suggest that CTE shares clinical symptoms with Parkinson's disease, Alzheimer's disease (AD), and mild cognitive impairment (MCI) [16–19].

The epidemiological dimensions of CTE remain largely unclear due to the limitations of current diagnostic systems. Nevertheless, the influence of concussions and sub-concussions on cognitive and physiological decline is well established [20,21]; in fact, athletes exposed to head impacts are at increased risk of developing neurodegenerative diseases such as mild traumatic brain injury, CTE or DP [22]. A quantitative electroencephalogram (EEG) study showed that patients with a history of traumatic brain injury had altered EEG patterns compared to healthy subjects, with increased theta band power and decreased alpha band activity [23].

A nonlinear analysis of EEG signals in American football athletes, conducted by Munia et al., examined the effects of concussions [24]. This study found differences in EEG abnormalities in athletes with a history of concussion compared to those without, using nonlinear metrics such as approximate entropy and the Hurst exponent. These findings suggest that nonlinear data analysis could be an effective predictor of repeated head impact accumulation in asymptomatic subjects.

Consequently, our research aims to explore the effects of concussion in boxers using both linear and nonlinear EEG data analysis. Besides traditional frequency content analysis via normalized power spectral density (nPSD), three different nonlinear methods were used: (i) the power law exponent (PLE) in contrast to linear nPSD results; (ii) the detrended fluctuation analysis (DFA) alongside the Hurst exponent; and (iii) multiscale entropy (MSE) compared to the approximate entropy measure. Comparing these nonlinear approaches with previously documented findings [23,24], the aim was to elucidate additional insights provided by nonlinear EEG analysis. These findings could lead to future developments that include potential cost reductions in clinical settings, enhanced understanding of the disease's pathogenesis and progression, and the ability to predict the onset of a malignant process, thus enabling early preventive interventions to halt progression or inform decisions regarding the continuation of an athletic career.

METHODS

Subjects and study design

Twenty-one boxers across different weight classes and years of activity were selected for this study, with the following characteristics (mean ± SD): age, 28.38 ± 5.5 years; weight class, 67.55 ± 8.90 kg; years of activity, 6.76 ± 5.45 years; education level, 14.19 ± 3.08 years.

The participants were divided into two groups. The advanced group comprised boxers who had participated in at least 25 fights and had a minimum of 5 years of boxing experience (mean ± SD): age, 30.60 ± 5.02 years; weight class, 66.25 ± 8.19 kg; years of activity, 10.55 ± 5.78 years; education level, 14.50 ± 4.12 years. The beginners group comprised individuals with (mean ± SD) age, 26.36 ± 5.33 years; weight class, 66.73 ± 9.73 kg; years of activity, 3.32 ± 1.38 years; education level, 13.91 ± 1.87 years.

An interview was conducted to document the number of concussions sustained during their careers (concussion count 0.91 ± 0.83). Cognitive assessments were also administered to confirm that the boxers were cognitively asymptomatic, using the Montreal Cognitive Assessment (MoCA) (24.46 ± 2.30) and the Frontal Assessment Battery (FAB) (16.37 ± 1.77); the scores were corrected according to age and education [25,26].

EEG recordings

The EEG signals were recorded using the International 10–20 System, with 19 electrodes placed on the subject's scalp. Two

sessions of resting state EEG were recorded: a 7-min eyes-closed (EC) session and another 7-min eyes-open (EO) session. The ground electrode was positioned at the frontal central channel (FCz), and a mastoid electrode served as a reference. At the same time, electrooculogram activity was collected using a bipolar electrode to mitigate EEG artefacts caused by eye movements. The contact impedance of each electrode was kept below 10 kΩ and balanced across channels (time constant 0.3 s). The EEG data were collected at a sampling rate of 2048 Hz and digitized using a 16-bit analogue-to-digital converter.

All data underwent off-line analysis in MATLAB (version 9.1, The Mathworks, Natick, MA, USA), where they were preprocessed to eliminate movement and power-line artefacts, thereby enhancing the signal's informative portions and minimizing the influence of electrocardiographic and electrooculogram activities. Additionally, a fourth-order Butterworth notch filter described as zero-phase was employed using the 'filtfilt' MATLAB function to prevent phase distortion and remove line noise at 50 Hz. A normalization procedure was implemented to reduce the variability of the EEG signals. Specifically, the signals were band-pass filtered using a fourth-order Butterworth filter with cut-off frequencies from 0.5 to 120 Hz, and artefacts were removed using independent components analysis.

Linear and nonlinear analyses

The preprocessed EEGs were divided into 60-s epochs and both linear and nonlinear measures were computed independently for all electrodes and averaged across the epochs. To facilitate the interpretation of the results, for each selected parameter consideration was given to (i) the average value on the whole electrodes and (ii) the average value on the electrodes divided into cortical regions: left frontal (LF: Fp1–F3–F7), right frontal (RF: Fp2–F4–F8), left temporal (LT: T3–T5), right temporal (RT: T4–T6), left centro-temporal (LCT: C3–T3), right centro-temporal (RCT: C4–T4), left parieto-occipital (LPO: P3–O1), right parieto-occipital (RPO: P4–02), left fronto-temporal (LFT: F3–F7–T3–T5), right fronto-temporal (RFT: F4–F8–T4–T6) and *z*-axis (Z: Fz–Cz–Pz).

The nPSD was estimated within the δ (2–4 Hz), θ (4–8 Hz), α (8–13 Hz) and β (13–30 Hz) frequency ranges. In detail, the power spectrum (PSD) was computed in the 1–45 Hz frequency band by applying the modified Welch periodogram [27] on 1-s Hamming windowed segments with 50% overlap, and the nPSD measure was obtained as follows:

$$\mathrm{nPSD} = \frac{1}{F_2 - F_1}\int_{f_1}^{f_2} \mathrm{PSD}(f)\mathrm{d}f$$

where $F_2 - F_1$ represents the frequency range over which the total spectrum was computed, that is, 1–45 Hz, f_1 and f_2 are the boundary frequencies over which the specific nPSD measure was estimated, and PSD(f) is the PSD at the frequency f [28].

On the other hand, the selected nonlinear algorithms considered are the following.

(i) PLE describes changes in the scale-free behaviour of the signal. The measure is obtained from the slope of the regression line computed on the PSD of the EEGs in log–log coordinates in the frequency bands 1–3.5 Hz, 4–7 Hz, 8–12 Hz and 13–35 Hz and goes beyond the classic linear measurement. Indeed, the PLE represents the contribution of the non-oscillatory components in the EEGs, usually not highlighted by the linear spectral analysis performed through the PSD. In order to highlight such components and to avoid the influence of those characterized by rhythmic behaviour, a peak removal operation was performed as suggested by the work of Colombo et al. [29].

(ii) DFA describes the degree of signal self-similarity expressed as the slope of a regression line calculated from the root-mean-square fluctuations of the signals in log–log coordinates. The fluctuations are extracted from the integrated and detrended signals at different observation windows [30]. The regression line is then computed by considering in log–log coordinates how the fluctuations change against the increasing size of the observation windows.

(iii) It is worth underlining that, from an applicative point of view, what seems to reflect neuronal activity in its dynamic nature are the so-called long range temporal correlations (LRTC) present in the time series [31]. For this reason, it was decided to estimate the LRTC measure, which consists of applying the DFA procedure to the amplitude envelopes of the EEG oscillatory activity, extracted by applying the band-pass filter (finite impulse response filter, order 2000 and Hamming window) in the specific frequency band of interest and then the Hilbert transform [31]. In this case, the considered frequency ranges were θ (4–8 Hz), α (8–13 Hz), low-β (13–20 Hz) and high-β (20–30 Hz).

(iv) MSE estimates the sample entropy index (SampEn) on different scales to quantify the degree of intrinsic randomness in the signals. The SampEn computes the conditional probability that two similar sequences of m points remain similar at point $m+1$ [32]. Thus, by considering different EEG sequences and by computing SampEn for each of them [33], the MSE curve is obtained and can be evaluated in terms of slopes. In detail, the sequences result through the coarse-grained procedure [33], a method that generates a new time series by considering the average of τ consecutive samples of the original signal, where τ is defined as a scale factor. As the τ value increases, different sequences are obtained. In this work, the number of scale factors considered is 30 and the MSE parameter was evaluated both at low (l-MSE with $\tau < 8$) and at high (h-MSE with $\tau > 8$) scale factors, whilst the parameters for the SampEn application are set to $m = 2$ and $r = 0.2$ times the standard deviation of the given signals.

Statistical analysis

First, an analysis was conducted to determine whether there were differences between groups based on neuropsychological data and level of expertise. In this context, an independent samples t test

(Mann–Whitney *U*) was used for the nonparametric distribution (Shapiro–Wilk, $p<0.05$). The Mann–Whitney *U* test was used to compare the two groups: beginners and advanced.

A nonlinear analysis was applied using LRTC within the frequency bands 4–7 Hz, 8–12 Hz, 13–20 Hz and 21–30 Hz for both EO and EC conditions. Each channel (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2) was analysed and the Mann–Whitney *U* test was applied. The same methods were used to analyse MSE at low frequencies (l-MSE) and high frequencies (h-MSE), as well as in PLE. Statistical significance was set at $\alpha=0.05$.

RESULTS

No significant differences were found in cognitive tests between the two groups (MoCA $p=0.287$; FAB $p=0.911$). However, significant differences between groups were observed in the nPSD in the frequency ranges 2–4 Hz, 4–7 Hz and 8–13 Hz during the EC condition. The mean PSD decreased in advanced boxers across all channels within the 4–7 Hz and 8–13 Hz frequency bands ($p=0.013$, $p=0.003$) (Figure 1) and in LF ($p=0.038$), LFT ($p=0.023$) and Z ($p=0.028$) in the 1–3.5 Hz frequency band (Figure 2). No significant differences in nPSD were found during the EO condition, whilst PLE in the F3 channel decreased during the EC condition in advanced boxers compared to beginners (F3 $p=0.010$) (Figure 3). No correlation was found between the FAB test and the F3 channel in the PLE EC condition (Spearman's rho 0.260, *p* value 0.866). Regarding LRTC, a significant decrease was observed in the 4–7 Hz and 13–20 Hz frequency bands in advanced boxers, especially in the F3 channel during the EO condition (4–7 Hz, F3 $p=0.036$; 13–20 Hz, F3 $p=0.036$) (Figure 4). No significant differences were observed in LRTC during EC EEG recording. Analysis of the MSE for each channel revealed a significant increase in low frequencies within the advanced group, which was particularly evident at the F3 and Fp1 electrodes during the EC condition (F3 $p=0.024$; Fp1 $p=0.043$) (Figure 5). Conversely, in the advanced group a decrease in high frequencies was observed at the O1 and O2 electrodes during the EO condition (O1 $p=0.029$; O2 $p=0.036$) (Figure 6).

DISCUSSION

The goal of our research was to investigate the effects of concussion in boxers using linear and nonlinear EEG data analysis. It was found that mean PSD and PLE significantly decreased in advanced boxers, whilst MSE increased at low frequencies and decreased at high frequencies compared to beginner boxers.

Nonlinear analysis of brain signals showed similar changes to those observed in the early stages of AD [34], which may have similar brain signals to asymptomatic boxers. AD is a neurodegenerative dementia and includes many symptoms common to DP [30]. In AD patients, local synaptic disruptions, due to the aggregation of pathological proteins in the brain, form amyloid plaques and neurofibrillary tangles [35,36], which can lead to impaired information processing between neurons. Vyšata et al. found that an overall EEG decrease in the power law exponent was associated with AD [37]. Furthermore, Stam et al. observed a decrease in synchronization and spontaneous fluctuations in the lower alpha and beta bands in AD patients [38].

The decrease in LRTC in the frequency bands 4–7 Hz and 13–20 Hz in channel F3 of advanced boxers could represent greater

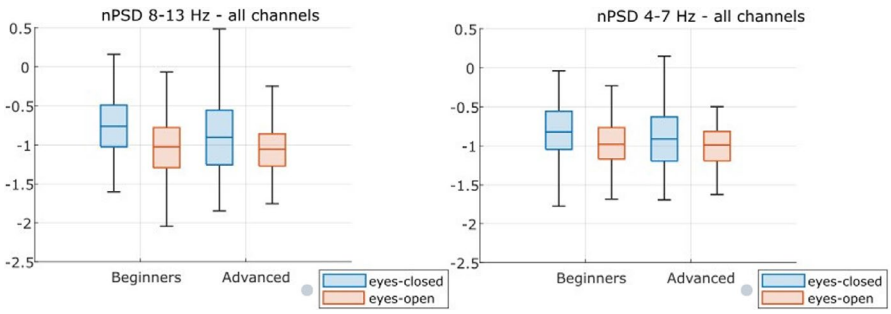


FIGURE 1 nPSD, all channels, 4–7 Hz and 8–13 Hz ($p=0.013$, $p=0.003$).

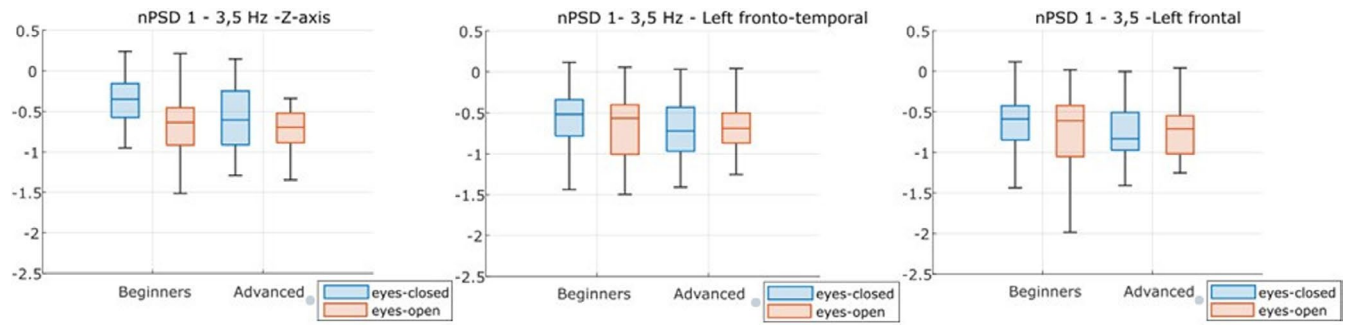


FIGURE 2 nPSD, 3.5 Hz frequency band LF ($p=0.038$), LFT ($p=0.023$) and Z ($p=0.028$).

regularity of the signal. A loss of complexity in the biological signal may represent less information transmission between neurons in AD [35,36].

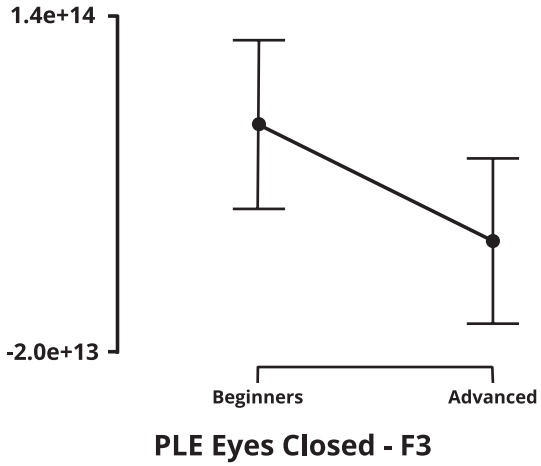


FIGURE 3 PLE, eyes closed F3 ($p=0.010$).

During the linear analysis of the nPSD, decreased mean power was found in the advanced group during the EC condition at the 2–4 Hz (LF, LFT, Z), 4–7 Hz and 8–13 Hz frequency bands (all channels). These results are comparable to the decreases in spectral density observed in AD. Changes in the 8–13 Hz band, observed during the EC condition, can be explained, at least in part, by the well-known desynchronization of alpha power upon opening the eyes. However, in this study, two different groups of boxers with different experiences were compared, and some of the nonlinear analyses performed are not influenced by PSD at all.

Multiscale entropy methods have been used as potential biomarkers of AD pathology and cognitive decline [39,40]. Entropy in EEG signals from AD patients was observed to decrease on short scales but increase on long scales compared to healthy subjects. The lower entropy values in AD and MCI showed a relative conservation of coarse-grained entropy and a selective loss in fine-grained entropy [39]. These multiscale temporal features could be related to the functional interaction and neural structural limitations observed in individuals with dementia [41].

FIGURE 4 LRTC, F3 eyes open, 4–7 Hz ($p=0.036$); 13–20 Hz ($p=0.036$).

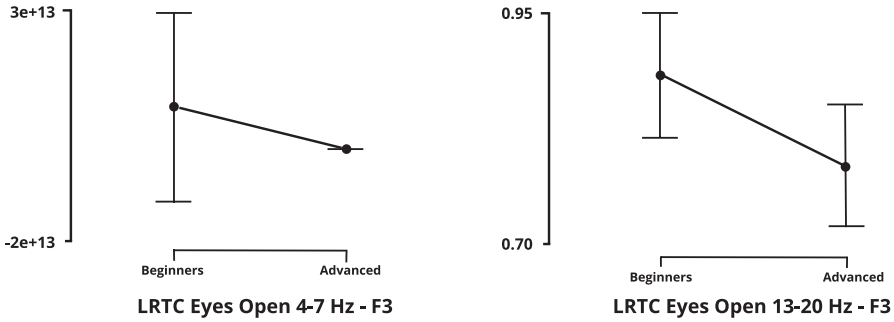


FIGURE 5 MSE low frequencies, eyes closed Fp1 ($p=0.043$); F3 ($p=0.024$).

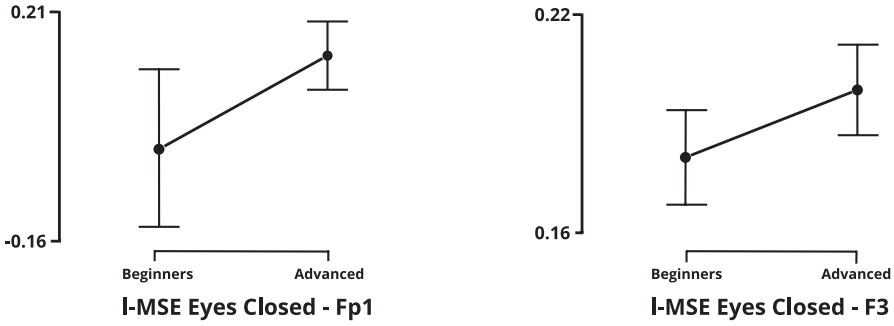
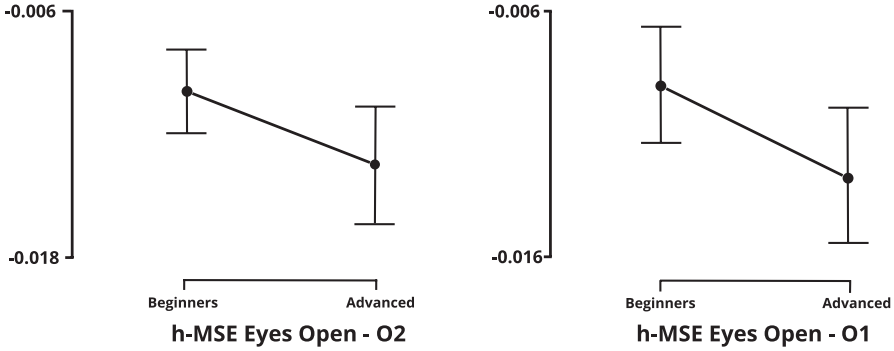


FIGURE 6 MSE high frequencies, eyes open O2 ($p=0.029$); O1 ($p=0.036$).



Two weighted scales were created to measure the low frequencies (1–8 short scales) and the high frequencies (9–20 long scales). The l-MSE in advanced boxers increased the flattening of the fine-grained entropy slope, whilst in h-MSE the coarse-grained entropy in advanced boxers decreased the steepness and complexity; these results are consistent with those of Mizuno et al. [39].

In advanced boxers, a significant increase in l-MSE was found, especially in the frontal lobe F3, and a decrease in h-MSE in the occipital lobes O1 and O2, whilst in AD the affected area is mostly in the temporal regions. Exact similarities with the predementia stage could not be determined. In the MCI stage, short-term memory associated with the medial temporal lobe is reduced, but the lateral temporal and parietal lobes are also affected. In the moderate stage of AD, the similarities increase compared to boxers in advanced stage. In fact, there is a loss of complexity of the frontal lobe in moderate AD, and the occipital lobe also deteriorates in several AD cases [42,43]. The greatest regularity and loss of complexity were associated with a decrease in brain dynamic complexity and, as expected, with a decrease in EEG signal complexity from subjective cognitive impairment to MCI to AD [44]. Changes in these EEG signals originating from frontal areas can also be explained by the pathophysiology of the so-called DP, in which the frontal white matter showed signs of glial tau inclusions, involving both astrocytes and oligodendrocytes that were involved and secondarily spread to other brain regions [45,46].

From a neuropsychological perspective, no significant differences in cognitive tests between the two groups were found; the lack of differences could be due to a ceiling effect. Furthermore, it was interesting that the athletes in our study were asymptomatic, and no correlation was found between the F3 channels in the PLE EC condition and the FAB test. Previous imaging and neurophysiological studies have shown that white matter and neurophysiological changes occur in tackle football players in the absence of cognitive and neuromotor impairments, suggesting that clinical neuropsychological deficits are more difficult to detect [47]. In addition, the FAB test is sensitive to the progression of the disease and is therefore suitable for monitoring the clinical progression of dementia. However, it may not be sensitive for detecting CTE in asymptomatic athletes. Therefore, more sophisticated neuropsychological testing should be used. In conclusion, our data suggest that nonlinear EEG data analysis could be a potential neurophysiological biomarker for the asymptomatic phase of CTE and could be useful for monitoring health status during the career of athletes, to reduce the risk of future neurological injuries.

AUTHOR CONTRIBUTIONS

Renato De Donato: conceptualization; investigation; writing—original draft preparation. Natale Vincenzo Maiorana: investigation; writing—review and editing. Maurizio Vergari: investigation. Angelica De Sandi: investigation. Anisa Naci; investigation. Giada Aglieco: investigation. Tommaso Albizzati: investigation; writing—review and editing. Matteo Guidetti: investigation. Rosanna Ferrara: conceptualization; methodology; formal analysis; writing—review and editing. Tommaso Bocci: writing—review and editing. Sergio Barbieri: writing—review and editing. Roberta Ferrucci: conceptualization; investigation; writing—review and editing; formal analysis; funding acquisition. Alberto Priori: conceptualization; project administration; funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Datasets related to the present study are available upon reasonable request from interested researchers.

ETHIC STATEMENT

The protocol and procedures were approved by the local Institutional Review Board. The procedures were conducted in accordance with the Declaration of Helsinki. All participants provided informed consent.

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