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ORIGINAL ARTICLE

Approximate entropy analysis across electroencephalographic rhythmic frequency bands during physiological aging of human brain

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Abstract Aging is the inevitable biological process that results in a progressive structural and functional decline associated with alterations in the resting/task-related brain activity, morphology, plasticity, and functionality. In the present study, we analyzed the effects of physiological aging on the human brain through entropy measures of electroencephalographic (EEG) signals. One hundred sixty-one participants were recruited and divided according to their age into young ($n=72$) and elderly ($n=89$) groups. Approximate entropy (ApEn) values were calculated in each participant for each EEG recording channel and both for the total EEG spectrum and for each of the main EEG frequency rhythms: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–11 Hz), alpha 2 (11–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–45 Hz), to identify eventual statistical differences between young and elderly. To demonstrate that the ApEn represents the age-related brain changes, the computed ApEn values were used as features in an age-related classification of subjects (young vs elderly), through linear, quadratic, and cubic support vector machine (SVM). Topographic maps of the statistical results showed statistically significant difference between the ApEn values of the two groups found in the total spectrum and in delta, theta, beta 2, and gamma. The classifiers (linear, quadratic, and cubic SVMs) revealed high levels of accuracy (respectively 93.20 ± 0.37, 93.16 ± 0.30, 90.62 ± 0.62) and area under the curve (respectively 0.95, 0.94, 0.93). ApEn seems to be a powerful, very sensitive–specific measure for the study of cognitive decline and global cortical alteration/degeneration in the elderly EEG activity.

Keywords Approximate entropy · Frequency bands · Aging · Machine learning · Support vector machine · Electroencephalography

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Introduction

Aging is a "persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration" [1]. This definition has been used many times; however, it was only a generalization of an intricate process. Over time other numerous descriptions have been given, e.g., the word "deterioration" was substituted with the term "adaptation" [2].

Studying how the brain changes during aging is crucial for several reasons. Firstly, a better

understanding of how the neurobiology behind aging as well as some brain modifications can influence cognitive functions can be obtained [3]. Secondly, by studying healthy elderly people, it is possible to understand and identify brain age-related diseases, such as Alzheimer's [4]. In fact, to date, age is the main risk factor for major debilitating conditions, including neurodegenerative diseases [5]. The brain seems to be particularly sensitive to the aging process since the appearance of neurodegenerative diseases is exponential with the aging. Furthermore, almost all aged brains show distinctive traits that are directly related to the neurodegenerative processes [6].

Over the years, functional neuroimaging approaches such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), functional near-infrared spectroscopy (fNIRS), magnetoencephalography (MEG), and electroencephalography (EEG) have allowed the non-invasive assessment of functional changes in the aging brain [7]. Among these techniques, EEG is a non-invasive approach, widely and easily used in clinical settings [8], for its low cost compared to other systems, for the lack of emission of radiation or production of noise due to strong magnetic fields, that respectively impact PET and fMRI [9]. In addition, the high temporal resolution (milliseconds) allows the investigation of the almost instantaneous dynamics of neural activity underlying cognitive processing and age-related changes [9].

To date, numerous EEG studies have explored the effects of aging on brain activity especially during resting state condition [7, 9, 10]. Physiological changes have been characterized as a progressive alteration in the frequency, power, and distribution of brain waves rhythmic oscillations; in particular, a progressive slowing with an increase in power in the delta (2–4 Hz) and theta (4–8 Hz) frequency ranges and a decrease in alpha (8–13 Hz) and beta power (13–30 Hz) have been observed in healthy aging [9].

Furthermore, additional mathematical models have been recently employed to describe brain architecture and quantify its complexity. Among these approaches, functional connectivity measures have emerged; in particular graph theory indexes have been used to analyze EEG data for the investigation of network's alterations during aging [11–13].

However, from the idea that the human brain has been shown to exhibit some kind of non-linear chaotic behavior [14], over time it was considered reasonable to apply methods from the theory of non-linear dynamics to the EEG signal in order to detect its variability. One non-linear approach to determine the non-linearities of EEG is a measure based on the ordinal patterns of recorded times series, namely the *entropy*. Initially, the term "entropy" was introduced in thermodynamics in the nineteenth century, and only later in 1948, this measure was adapted for information theory and signal analysis [15]. Entropy was defined as a measure of information comprised in a given amount of signals and represents and describes the irregularity, complexity, or unpredictability characteristics of a signal [14]. Moreover, as neural systems have been shown to exhibit some kind of non-linear chaotic behavior, entropy measures can be successfully applied to the EEG signal to detect its variability or complexity. The variability and complexity emerge from the interplay between individual neurons and their neuronal circuits and tend to extend over wide spatiotemporal scales in the brain [16]. Starting from this consideration, the entropic brain hypothesis by Carhart-Harris takes hold [17], suggesting that any given mental state can be indexed by a quantitative measure of the magnitude of entropy as a measure to describe the spontaneous brain activity, for example, recorded with EEG [18–23].

So, entropy represents an interesting approach for EEG analysis, and it can be used to quantify brain functions and alteration across brain areas, for example, related to the aging effects; however, to date only few studies exist in the literature describing this process. The first research, in 2009, by Takahashi and colleagues [18] revealed that the application of multiscale entropy (MSE) to the EEG signal is a possible approach for studying age-related changes in brain function; their results showed that after a phonic stimulation, an increase in complexity of MSE was found only in young subjects, instead absent in elderlies. McIntosh and colleagues [19] demonstrated the presence of age-dependent changes in MSE with age, indicating an increase in brain signal variability across the lifespan. More recently, Alù and colleagues [22] demonstrated that elderly subjects present higher approximate entropy (ApEn) values compared to the younger in central, parietal, and occipital areas of the brain, confirming that the entropy parameter can be a useful tool to characterize aging processes.

Within this theoretical frame, the present study aims to explore the EEG brain complexity differences between two groups, respectively of young and elderly subjects, in terms of ApEn. Among the above-mentioned entropy measures, the ApEn appears to be a non-linear complexity index that can be applied with good reproducibility to time series, it is almost unaffected by noise, and it detects the changes in underlying episodic behavior undetected by peak occurrences or amplitudes [24]. Moreover, ApEn has been extensively used in studies of physiologic time series to assess the degree of randomness [25]. For all the exposed reasons, ApEn could be extremely helpful in understanding brain aging, given the complex and dynamical characteristics of the cerebral system.

Furthermore, although the importance of the existing EEG biomarkers and their modulation across the typical EEG frequency bands in the aging process are widely known, still no one has studied the ApEn alteration in the EEG spectrum to delineate what happens in an elderly brain from this point of view. The novelty of the present paper has been to investigate the ApEn from the whole EEG spectrum (0.2–47 Hz) and from filtered EEG data using 7 frequency bands, namely delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–11 Hz), alpha 2 (11–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–45 Hz), in order to evaluate, for the first time, how this parameter can change during aging evaluating it across entire EEG frequency spectrum. Additionally, with the aim of testing if the ApEn represents a measure able to describe age-related changes occurring in the brain, the computed ApEn values were also used as features to perform an age-related classification of subjects employing three types of support vector machine (SVM) (linear, quadratic, and cubic).

Methods

Participants

A total of 161 healthy participants were recruited and divided according to their age in two groups. Seventy-two young subjects (38 female; mean age = 24.8, SE = 3.4; education = 14.3, SE = 2.6) and 89 older adults (47 female; mean age = 69.4, SE = 4.4; education = 10.9, SE = 3.7) compose respectively the young and the elderly group. Table 1 shows the demographic details of the two groups. Subjects with ongoing therapy with psychotropic or vasoactive medications and neurological or psychiatric disorder history were excluded from the study. All subjects have been classified as right-handed at the Handedness Questionnaire [26]. Following the World Medical Association Code of Ethics (1997), each participant accepted an informed consent, and the experimental method agreed with Declaration of Helsinki.

Table 1 Sex, age, and education of all subjects enrolled in the experiment

	Young ($n = 72$)	Elderly ($n = 89$)
Sex (M/F)	34/38	42/47
Age (mean ± *SE*)	24.8 ± 3.4	69.4 ± 4.4
Education (mean ± *SE*)	14.3 ± 2.6	10.9 ± 3.7

Data recordings and pre-processing

EEG recordings were obtained from a 32-channel system (Easycap, GmbH, Brain Products). The electrodes were placed on the scalp according to the Augmented International 10–20 system using the midfrontal Fpz electrode as the reference and one electrode as the ground; for these reasons, the number of valuable EEG electrodes is 31. Ocular movements and blinking were visually monitored using both vertical and horizontal EOG channels, although the removal of ocular artifacts was successfully conducted only in the later analysis phase using the Infomax ICA algorithm. Electrodes' impedance was kept under 5 kΩ, and the sampling rate was set up at 1000 Hz. An eyes-close (EC) resting state session of 6 min was recorded by each participant, while seated on a comfortably armchair in an electrically shielded, sound-damped and dimly lit room. The data were processed using a home-made MATLAB software, based on EEGLAB toolbox codes (Swartz Center for Computational Neurosciences, La Jolla, CA, USA) [27, 28]. The EEG data were down-sampled with a frequency rate of 512 Hz, and a band-pass finite impulse filter (FIR) was applied to extract data in the frequency range from 0.2 to 47 Hz. EEG continuous data were segmented in 2-s length epochs and trials with artifact activity (such as scalp muscle activity and cardiac activity), or aberrant waveforms were removed first by an expert data visual inspection, then

using the Infomax ICA algorithms [29], that decompose the signal in statistically independent component and complete the detection, cleaning, and rejection of epochs with artifacts [30–34]. After this inspection, about 5 min remained for each session.

Entropy

The complexity of brain activity was studied by entropy measure evaluated by approximate entropy (ApEn). The use of ApEn for complexity measures has many advantages: it maintains a good reproducibility when used with time series; it is almost unaffected by noise, and it detects changes in underlying episodic behavior undetected by peak occurrences or amplitudes [24].

ApEn values were computed, in each participant, for each channel and for each frequency band using homemade MATLAB software. Firstly, a value of ApEn was computed for each channel and each epoch in the following frequency bands: delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–11 Hz), alpha 2 (11–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–45 Hz). Finally, for each EEG recording, those values were averaged among the epochs [35] to obtain a single ApEn value for each channel in each frequency band. In order to compare the results obtained in the present study with those present in the literature, the same procedure was performed to compute the ApEn values in the total spectrum (0.2–47 Hz) [22, 23].

The homemade software estimates ApEn dimensionless values. The higher the value of ApEn, the more irregular and less predictable the signal is. On the other hand, the lower this value, the more periodic and stable the signal tends to be [23]. In the ApEn analysis, two input parameters need to be defined: a model length m and a tolerance factor r, also called similarity factor, used to identify a range of similarities between data points. In this study, m and r were set equal to the default MATLAB values: thus, $m=2$ and $r=0.2 * variance\ (x)$ [36–38] were used, in which x corresponds to an epoch of length of 2 s of a specific channel. The obtained ApEn values range from 0 (regular time series) to 2 (random time series) [39].

In particular, the calculation of ApEn is described as follows [40, 41]:

1. A point-by-point comparison is made between each data sequence of length m and all other sequences. If the distance between points is less than the tolerance factor r, a match is scored.

All the matches are counted as described by Expression (1):

$$N_i = \sum_{i=1, i\neq k}^{N} \left(\|Y_i - Y_k\|_\infty < r \right) \tag{1}$$

where Y_i is the m-dimensional vector sequence, defined as a delayed reconstruction of the time series$\{y(i)\} = y(1), y(2), \ldots, y(N)$, where i ranges from 1 to N, number of data points:

$$Y_i = \left[y(i), y(i+1), \ldots, y(i+m+1) \right] \tag{2}$$

2. The comparison is performed on each successive $m+1$-long sequence, starting form the first sequence of $m+1$ points, as shown in Eq. (2).
3. The number of matches is converted to a natural logarithm value and afterwards normalized by the number of data points (N):

$$\Phi_m = (N-m+1)^{-1} \sum_{i=1}^{N-m+1} \log\left(N_i\right) \tag{3}$$

Finally, the ApEn is calculated using the following expression:

$$ApEn = \phi_m - \phi_{m+1}. \tag{4}$$

Moreover, using the algorithm implemented in MATLAB, the topographic distribution of the ApEn values both in the total spectrum and in each frequency band was obtained for the young group and the elderly one. At each electrode was associated a single value of ApEn. The software computes the interpolation between the ApEn values of the electrodes and represents the entropy values by a color scale. In this way, it was possible to analyze the distribution and age-related modulation of entropy on the scalp, which represent one of the innovations of the present study compared with the literature.

The entropy concept

The concept of entropy was initially introduced in thermodynamics by Clausius and developed by Boltzmann and Gibbs in the course of nineteenth century.

Entropy was then adapted for information theory and signal analysis in 1948 by Claude Shannon who defined it as the level of information, surprise, uncertainty, or a "gradual decline into disorder" in a given amount of a signal [42]. This theory was then applied to the brain signal analysis starting from the hypothesis that entropy can be a powerful explanatory tool to describe any mental state, providing a quantitative index of the brain dynamic system's randomness or disorder [43]. Small fluctuations in brain entropy are natural, but according to Carhart-Harris' model, many brain states can be classified as "low entropy" or "high entropy" [17]. From the physics point of view, high entropy means high disorder and low energy: to maintain a structure, energy is required.

Following this line, to explain how entropy can facilitate the study and analysis of brain activity, it is useful to imagine the brain's neural population as a system that persists in a sort of firing baseline state, although this is obviously an oversimplification of how the brain may function. In response to a stimuli, or the presence of physiological or pathological aging conditions, the hypothesis is that the brain's neuronal population can deviate from its baseline state to a different firing state that may give rise to a less complex system (more regular firing pattern) or to a more complex one (neural activity is more random) [16].

Statistical evaluation

The two-tailed unpaired Student's t-test was performed to analyze the ApEn values to highlight the statistical differences in each frequency band (total, delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma) between groups (young, elderly). To account for multiple comparisons, the Bonferroni correction was performed on MATLAB. The function maintains the same threshold for the hypothesis rejection ($p < 0.05$) but changes the p-values of the statistical analysis according to the number of comparisons. The new p-values obtained are reported in Table 2.

Classification

To demonstrate that ApEn represents age-related changes in the brain, the computed ApEn values were used as features to perform an age-related classification of subjects. A classification procedure is a method to create a boundary between two or more classes that enables their best prediction from one or more feature vectors. The boundary arrangement is carried out according to an established criterion [44]. This rule depends on the type of the chosen classifier. For example, support vector machine (SVM), the most common method used with linear and non-linear problems in machine learning [45–47], constructs an optimal hyperplane based on the training data that best separate two or more classes [48]. To build the decision boundary among the classes and to optimize hyperparameters, a quadratic optimization problem needs to be solved [49]. To do this, the SVM classifier uses the sequential minimal optimization (SMO) algorithm. Unlike other methods, SMO chooses to solve, at every iteration of classifier training, the as small as possible optimization problem by decomposing the original problem into simpler sub-problems. In this way, it is solved quickly and analytically, significantly improving the computation time [50].

In this work, three different types of SVM were evaluated (linear, quadratic, and cubic SVM) using homemade scripts based on SVMs' implemented function on MATLAB. The linear SVM builds a linear hyperplane using a linear kernel $K\left(x_i, x_j\right) = x_i^T x_j$, given the observation $x_i, i = 1, \ldots, l$. Instead for quadratic and cubic SVM, a polynomial kernel was employed: $K\left(x_i, x_j\right) = \left(x_i^T x_j + 1\right)^d$, where d is the degree of the polynomial kernel. d is equal to 2 for quadratic SVM and to 3 for cubic SVM [51]. Quadratic and cubic kernel enables to model higher dimensional and non-linear models [20, 52].

Two different datasets were used for the classification. The first one consists of all the ApEn values obtained for each of the 31 recording channels and in each of the 7 frequency bands for a total of 217 features (31 channels × 7 frequency bands). The second database contains 21 features selected from the above dataset with an automatic feature selection technique called the stepwise regression function, which adds and removes terms from the initial model based on their significance in explaining the classification [53] in order to determine the best ApEn features that explain the data. There are three different variants of this technique. Forward selection starts from an empty model and then, based on a quality criterion, adds features; backward selection starts from all features and then, based on a quality criterion, removes features; the third variant is a combination of both. In high-dimensional problems, also a stopping criterion

Table 2 Significant *p*-values obtained after Bonferroni correction for each channel and in each frequency band

	Total	Delta	Theta	Alpha 1	Alpha 2	Beta 1	Beta 2	Gamma
Fp1	-	-	-	-	-	-	-	-
Fp2	-	-	-	-	-	-	-	-
AF7	-	-	-	-	-	-	-	-
AF8	-	0.034419	-	-	-	-	-	-
F7	-	-	-	-	-	-	-	-
F3	0.045618	-	-	-	-	-	-	0.003588
Fz	1.86E-06	-	0.035483	-	-	-	-	0.002459
F4	8.88E-06	-	-	-	-	-	-	0.017365
F8	-	0.00145	-	-	-	-	-	0.033302
FC5	-	-	0.024336	-	-	-	-	0.036875
FC1	7.38E-05	-	0.026024	-	-	-	-	0.041576
FC2	1.84E-06	-	0.016836	-	-	-	-	0.0236994
FC6	0.001513	0.008887	-	-	-	-	-	0.046002
T7	-	-	0.001656	-	-	-	-	-
C3	0.002459	-	0.030691	-	-	-	0.037925	0.041576
Cz	3.47E-05	-	0.003536	-	-	-	-	0.032632
C4	7.25E-07	-	0.015533	-	-	-	-	0.030968
T8	7.38E-05	0.0035288	0.021555	-	-	-	-	0.032632
CP5	0.045618	-	0.023193	-	-	-	0.004028	-
CP1	4.62E-05	-	0.026411	-	-	-	-	-
CP2	1.36E-06	-	0.012672	-	-	-	-	-
CP6	1.13E-07	-	0.024336	-	-	-	-	-
P7	-	0.03362	-	-	-	-	0.001698	-
P3	0.000215	-	-	-	-	-	-	-
Pz	2.29E-06	-	-	-	-	-	-	-
P4	1.86E-06	-	-	-	-	-	-	-
P8	2.09E-05	-	-	-	-	-	-	0.030657
PO7	-	0.0004723	-	-	-	-	-	-
PO8	0.000144	-	-	-	-	-	-	0.009817
O1	-	0.001409	-	-	-	-	-	-
O2	0.00194	0.000654	-	-	-	-	-	-

needs to be defined. A popular stopping criterion is no improvement in the quality assessment of the classifier. In the present work, a forward feature selection technique was applied. Considering all the possible combinations, it starts from an empty model and then adds at each iteration one variable at time based on its *p*-value obtained from an *F*-test that evaluate the statistical change of the sum squared error that results from adding the term. Unless the F-test *p*-value is lower than 0.05, the variable will be added to the model. So features with near-zero variance and significantly correlated features are removed from the model since they contribute complexity to the SVM without adding predictive power [54]. This selection procedure, together with the cross-validation technique, was employed also to avoid overfitting.

Indeed, for each SVM classifier, in order to evaluate the accuracy, a tenfold cross-validation was performed [33, 55, 56]. More specifically the dataset was randomly split into mutually exclusive and equal-sized 10 subsets, and for each subset, the classifier was trained using all the other subsets. In this way, 90% of the data was on the training set, and the rest 10% was on the test set. Moreover, to have an exhaustive model evaluation, the tenfold cross-validation was performed 100 times. This classification pipeline is explained in Fig. 1.

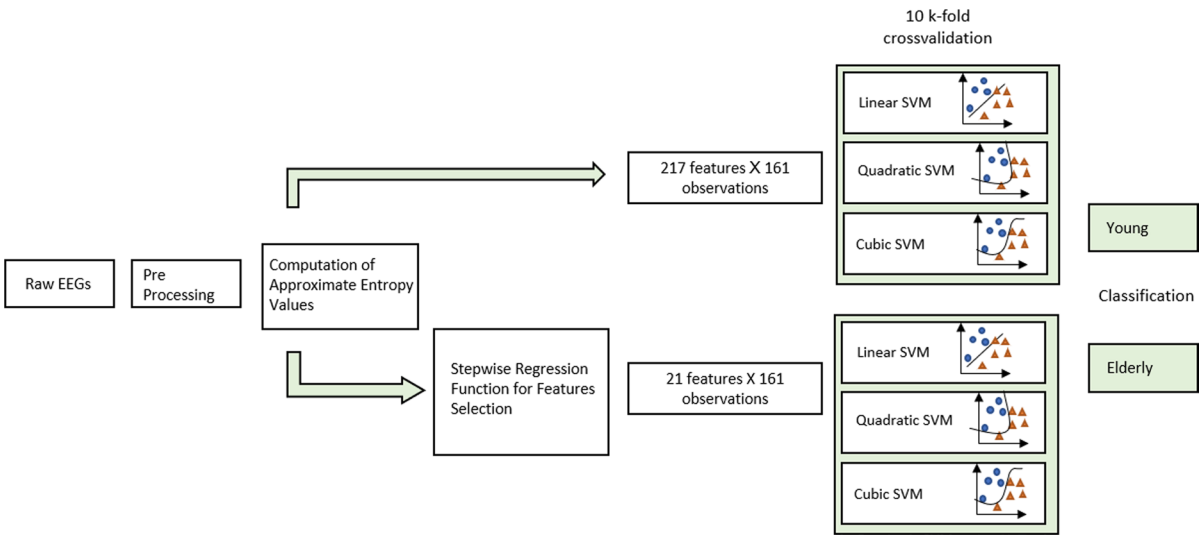

Fig. 1 Pipeline for the classification procedures of young and elderly subjects, starting from the raw EEGs to the computation of ApEn values for each channel and each frequency band for testing the performance of linear, quadratic, and cubic support vector machine classifiers. The two approaches which can be used are shown in the top line (where all 217 features have been used for the classification) and in the bottom line (where, after the feature selection, 21 features have been used for the classification)

The accuracy is computed as the mean of accuracy for all the 10-folds. In order to assess the variance between each fold, the standard deviation was also computed [33]. The same approach was followed to evaluate the specificity, sensitivity, area under the curve (AUC), and receiver operating characteristic (ROC) curve. Finally, the best classifier was selected based on the accuracy parameter, firstly because the latter correctly reflects the classification performance when the two classes are well balanced, as in our case, and secondly because the classification problem (elderly vs young) does not require to distinguish between a pathological and a non-pathological state (i.e., it does not require to distinguish between the amount of false negative or false positive).

Results

To investigate the difference between the young and elderly group, ApEn values were estimated for each participant and for each EEG frequency band in a resting state condition. For each frequency band and for the total spectrum, the topographical maps of the obtained ApEn values of the young and elderly and the distribution of the statistically significant differences between the two groups were also computed.

A statistically significant difference between the ApEn values of the two groups was found in the total spectrum and in the following frequency bands: delta, theta, beta 2, and gamma. The analysis of the total spectrum was performed to compare the results obtained in this work with the entropy studies present in the literature.

In the total ApEn, a statistically significant difference between the two groups was found in the centroparietal, right occipital, and right temporal regions. In all the three regions, the elderly group had a significantly higher ApEn values than the young one.

Moreover, in delta ApEn, results showed a significant difference in the left occipital and right frontotemporal brain areas. Additionally, the elderly group showed higher ApEn values in the left occipital region that the young one; instead, in the right frontoparietal region, the elderly revealed lower ApEn values than the young.

Regarding the theta ApEn, the elderly exhibited in the entire central region significantly higher ApEn value than the young. In the beta 2 ApEn, a significant difference between the two groups was found in the centrotemporal brain area. Particularly, the elderly

group displayed lower ApEn values than the young group.

Furthermore, in the gamma band, the elderly group showed significantly lower ApEn values in the frontocentral region than the young one.

Finally, no statistically significant differences between the two groups were found in the alpha 1, alpha 2, and beta 1 frequency bands.

All the topographic maps based on ApEn values and the statistical difference between the two groups are illustrated in Fig. 2. The significant *p*-values of the statistical results obtained with Bonferroni correction were reported for each electrode in Table 2.

For the classification process, each type of SVM classifier was performed using both all the ApEn values (i.e., the ApEn values obtained for each electrode and in each frequency band) and using only the most representative features. More specifically, in the latter case, only 21 features were selected and then used for the classification. The resulting performances of the best classifier, selected after 100 iterations, for the linear, quadratic, and cubic SVM, both before and after the features selection, are shown in Table 3. Each classifier's performance parameter (accuracy, AUC, specificity, and sensitivity) is reported in terms of mean value ± SE. For each type of SVM, the receiver operating characteristic (ROC) curve of the best classifier was calculated and illustrated in Fig. 3 with its 95% of confidence interval, computed over its 10-folds.

Discussion

Age is the main risk factor for major debilitating conditions, including neurodegenerative disease [6]. Since most people experience changes in cognitive functions and in macrostructural brain properties, by comparing the brains of young people and healthy elderly, a deeper comprehension of the neurobiological process of aging and brain cognitive changes can be obtained [3]. Moreover, by comparing elderly and young people, it is possible to better identify age-related pathology, especially Alzheimer's disease [4].

The aim of this work has been to achieve a better understanding of the effects of physiological aging on the neurobiological process and a deeper understanding of the brain's cognitive age-related changes. The ApEn values were calculated in the total spectrum and in seven main EEG frequency bands (delta, theta, alpha 1, alpha 2, beta 1, beta 2, and gamma) in order to detect changes in brain activity related to the aging process. Moreover, the topographic distributions of the ApEn values were also evaluated in the young and elderly group, thanks to the possibility to map the entropy values on the scalp.

The results, that have been reached in this study, can be divided into two principal findings: in the total EEG spectrum and in the lower frequency bands (delta and theta), higher ApEn values in the elderly group compared to the young were found; vice versa, in the higher frequency bands (beta 2 and gamma), lower ApEn values were obtained in the elderly group with respect to the young one.

Particularly, in the total EEG spectrum, the increase of entropy values is statistically significant in the centroparietal, right occipital, and right temporal regions. In the delta frequency band, a statistically significant difference is found in the left occipital brain areas, where the elderlies show higher entropy values than the young subjects, and in the right frontoparietal regions, where instead elderlies exhibit lower entropy values than the young. Regarding the theta frequency band, elderlies exhibit, in the entire central region, significantly higher entropy values than the young.

On the other hand, in the higher frequencies, the decrease of entropy values in the elderly group is statistically significant in the left centrotemporal brain area, regarding the beta 2 frequency band, and in the frontocentral region, regarding the gamma frequency band.

Finally, in order to demonstrate the relevance of entropy measures as an optimal biomarker sensitive to the effects of age-related changes on the brain activity and functionality, a procedure of classification was also realized. In our study, we have employed the support vector machine classifier. The latter is widely used for classification in the field of neuroscience. It solves the classification problem by identifying the best reproducible hyperplane (i.e., the boundary between the features of the two classes) that maximizes the distance between the support vector of both classes' features. There are many advantages reported in the literature in using this type of classifier. Firstly, SVM allows to optimize both the accuracy and the reproducibility (i.e., the classifier is generalizable to new data) [54], reducing even the possibility to occur in overfitting. Another fundamental characteristic is

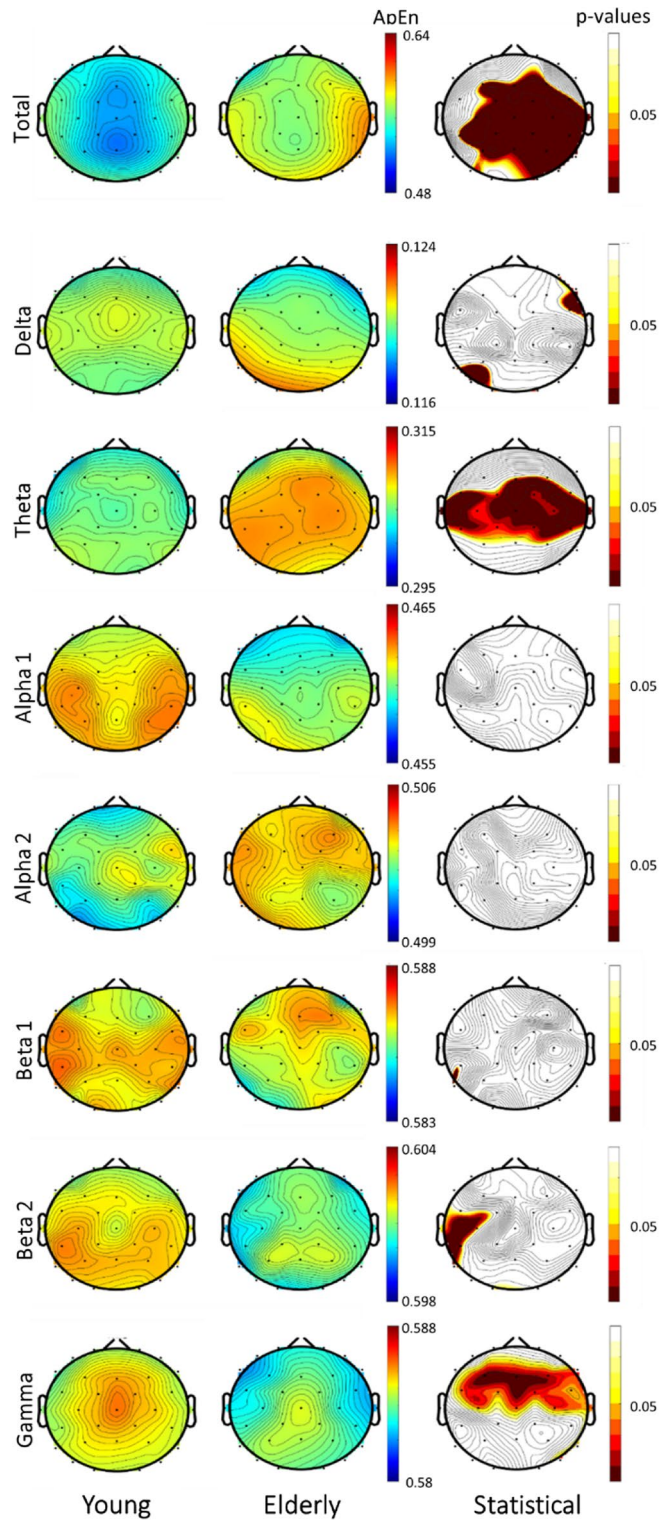

Fig. 2 Topography based on the ApEn values and statistically significant difference between the two group. Each row shows the ApEn across EEG band (total, delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma). The ApEn values of young and elderly groups are shown, respectively, in the first and second column. The entropy value is represented by a color scale, namely the more red, the higher the ApEn value, and the more blue, the lower the ApEn value. For every frequency band, the colorbar limits were set from the minimum of the ApEn values of the two groups to the maximum of the ApEn values of the two groups ± 2*Standard Deviation (SD). The last column represents the distribution of the *p*-values between the two groups obtained with Bonferroni correction

Table 3 Linear, quadratic, and cubic SVM performance parameter values represented by mean ± SE before and after the feature selection

Classifier	*Accuracy (%)*	*AUC*	*Specificity (%)*	*Sensitivity (%)*
All features				
SVM linear	89.45 ± 2.46	0.89	91.96 ± 2.00	87.78 ± 3.1
SVM quadratic	89.45 ± 2.56	0.93	88.92 ± 2.77	89.86 ± 3.61
SVM cubic	90.11 ± 2.14	0.92	93.21 ± 2.59	87.78 ± 2.26
After the feature selection				
SVM linear	93.20 ± 1.42	0.96	91.40 ± 1.31	94.30 ± 2.25
SVM quadratic	93.16 ± 1.81	0.95	94.29 ± 1.37	92.2 ± 2.38
SVM cubic	90.62 ± 1.86	0.95	90.0 ± 2.24	90.97 ± 3.64

that SVM is very efficient compared to other classifiers in high-dimensional space. In fact, since the decision boundary is identified using the kernel methods, the computing complexity does not increase in high-dimensional space [57]. The latter is a very interesting advantage since the classification performed in our study included a high number of features. Finally, the SVM can be considered a very stable classification method. Indeed, since a small change of the data does not greatly affect the hyperplane, by removing one or more features, the classification performances do not significantly change. In the literature, three different types of SVM are mainly used: linear, quadratic, and cubic SVM. We decide to test all of them to identify which one of the three returned the best performance for the automatic detection of the young versus elderly group. The results of the present paper revealed that the three SVMs showed optimal classification performances that increase after the application of a feature's reduction strategies. In fact, not only cubic but also quadratic and linear SVM exhibit high accuracy, respectively of 90.62 ± 1.86 (%), 93.16 ± 1.81 (%), and 93.20 ± 1.42 (%) indicating that the entropy has an optimal capability in the detection of age changes in brain activity.

Regarding the first result of the present research, it has shown that aging is associated with an increase of the total spectrum ApEn in the frontocentral, centroparietal, and occipital areas. This confirms the previous findings by Alù and collaborators [22], who showed that elderly subjects presented higher entropy than young participants in the central parietal and occipital brain areas, justifying that it could reflect a reduced synchronization of neural networks caused by aging. Furthermore, in line with this result, previous research found the cause of the changes in anatomic and functional connectivity as well as in the alteration of biophysical properties such as the reduction of the gray matter and the decrease of skull conductance [58]. All the mentioned reasons lead consequently to the increase of signal variability [58].

Actually, our hypothesis was that the alteration in the global entropy can reflect the reduced ability of the brain activity to sustain the typical EEG rhythmicity. For these reasons, it could be crucial to investigate what really happen at the EEG frequency rhythm level.

The entropy alterations, or rather the increase, occurring in delta and theta bands can be explained by the numerous findings of the current literature in which aging is associated with clear changes in delta and theta rhythms, in particular in the power spectral density [9, 59].The alteration of low-frequency bands was considered a marker of brain sufferance, cognitive dysfunction, and mental deterioration especially when their synchronization appears in a waking brain [60]. In particular, variations in theta activity in the elderly can suggest that brain aging alters the cortical circuitries of that specific band dynamics, leading to impairment in some brain functions, such as focused attentional and working memory processing [61]. Additionally, some studies, in which graph analysis was employed, showed that delta and theta connectivity's increase might reflect a process of progressive disconnection of the aging brain that could appear as a loss of communication efficiency between different areas of the brain [56, 62] and as a more chaotic EEG signal too, explaining an increase in *entropy*.

Concerning the high-frequency bands findings in beta 2 and gamma, the latter exhibit the opposite behavior compared to the low-frequency bands, showing a decrease of ApEn values in the elderly with respect to younger participants. Aging can be effectively related to a reduction in beta power

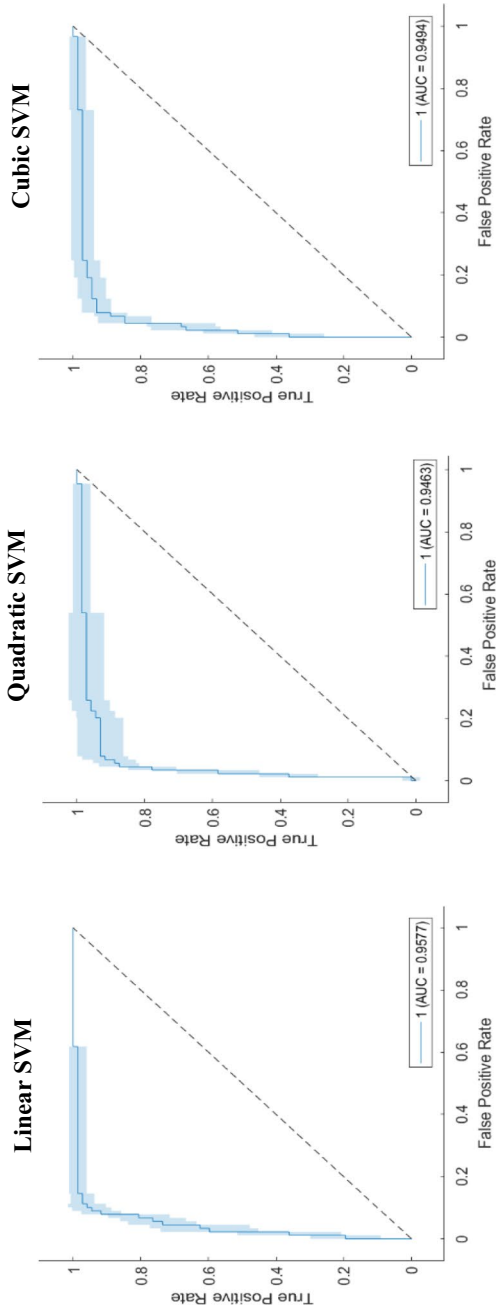

Fig. 3 Average receiving operating characteristic (ROC) curves and their confidence intervals at 95% level, illustrating the classification of the 161 participants based on the features selected by stepwise regression performed by linear, quadratic, and cubic SVM. The area under the curve (AUC) was, respectively, 0.95, 0.94, and 0.93, indicating an optimal classification accuracy

spectral density [9]; as in numerous studies [63, 64], beta synchronization was correlated with better cognitive skills, particularly the higher the beta power, the higher the cognitive performances. Specifically, EEG beta 2 power was found positively correlated with cognitive abilities in the study of Wang and collaborators [65], and it resulted to have an important role in cognitive processes in the research of Guntekin and colleagues [66]. Moreover, gamma rhythm was also demonstrated to have an important link with aging [67, 68]. In fact, several cognitive functions have been linked to the gamma band, like working memory and attentional processes. Abnormalities in gamma frequency are associated with the wrong processing of information in cognition and might reflect the need for more resources for efficient network integration [68].

Furthermore, gamma connectivity has been demonstrated to be a biomarker of working memory impairment in physiological aging. For example, in the study of Vecchio and colleagues [69], gamma connectivity, measured by Small World properties, positively correlates with memory, namely higher Small World characteristics in EEG gamma frequency during the resting state, better performance in short-term memory, evaluated by specific memory tests.

Additionally, the entire high-frequency spectrum (beta 2 and gamma) was found related to hippocampus atrophy [70, 71]. It was demonstrated that the atrophy of the hippocampus, which could lead to memory impairments, is correlated to the modulation of high-frequency Small World characteristics. Moreover, the elderly tend to show less complex networks than younger participants; in particular, in older subjects, a decrease of high EEG frequency global integration values and thus a decrease in randomness were revealed [70, 71], although Vecchio and collaborators did not find any differences in graph metrics in beta 2 and gamma between young, adult, and elderly participant [11]. Some of the results, obtained from graph analysis, although with a slightly different meaning, are in line with the present study, which clearly shows a decrease in entropy values, so a less chaotic signal in beta 2 and gamma bands. Additionally, the low entropy values in Gamma bands have been found in the frontal areas of the scalp. This localization is in agreement with other previous studies [72, 73] in which a synchronization of gamma bands in the frontal cortex, in particular in Brodmann area 9, was found.

However, to date, the studies widespread in the literature, across the EEG spectrum, are those that demonstrated alterations by means of power spectral density and functional connectivity. In this sense, the study of entropy across frequency bands is still in its infancy. Even if other studies have previously analyzed the modulation of ApEn across the EEG spectrum [74–77], this is the first time it has been tested to distinguish an elderly brain from a younger brain.

Through the machine learning approach and thanks to the SVM classification, it was evident as the parameters derived from ApEn values are highly capable of distinguishing between these two age-different population categories, reaching remarkable accuracy, sensitivity, and specificity values with three different classifiers. The underlying characteristics of EEG rhythms in terms of entropy contain relevant information on degenerative processes that normally occurred during aging.

To the best of our knowledge, this is the first study in which entropy parameters are evaluated across the typical EEG frequency bands to delineate the EEG complexity of a young and an old brain. Furthermore, for the first time, the entropy features are also used in a machine-learning context to classify elderlies with respect to young subjects. This study was conducted with a quite larger number of participants with respect to the current literature, demonstrating as approximate entropy seems to be a powerful measure for the detection of the age-related changes in the human brain. This measure appears to be a very sensitive and specific biomarker for the study of cognitive decline and global cortical alteration and degeneration in the elderly EEG activity.

Actually, the present research could be considered a preliminary analysis to test the use of entropy as an optimal biomarker for distinguishing age-related changes occurring in the brain. This is a starting point for using these types of parameters to distinguish also pathological conditions, such as neurodegenerative diseases, or intercept stages prior to the disease manifestation. Now, our main aim was to demonstrate as entropy (taken together the indexes both in the total EEG spectrum and in each frequency band) could be a powerful measure with very high levels of performance, and thus we believe that in the future, these parameters should be tested for the prediction, the diagnosis, and the prognosis of neurological

disorders, giving a more important contribution to clinical research.

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Data Availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interests The authors declare no competing interests.

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