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ORIGINAL RESEARCH

Electrophysiological Signatures of Alpha Coma

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Purpose: Recent research on quantitative EEG in coma has proposed several metrics correlating with consciousness level. However, the heterogeneous nature of coma can challenge the generalizability of these measures. This study investigates alpha-coma, an electroclinical pattern characterized by a widespread, nonreactive alpha rhythm often linked to poor outcomes. The aim was to quantify the electrophysiological features of alpha-coma and compare them to the alpha rhythm in awake controls, seeking clearer insights into quantitative EEG analysis in comatose states.

Methods: Fourteen alpha-coma patients were retrospectively selected from University Hospitals of Geneva and age-matched with 14 healthy control subjects from an open-source dataset. EEG data were preprocessed and analyzed to extract power spectra, spectral decay (aperiodic activity), sample entropy, and functional connectivity.

Results: Alpha-coma patients did not differ in alpha power but exhibited significantly higher levels of spectral decay ($p < 0.001$), suggesting a convergence toward an inhibitory state. Sample entropy was significantly higher in alpha-coma patients ($p = 0.01$), indicating an increase in the cortical complexity in alpha-coma compared with healthy subjects.

Conclusions: Alpha-coma shows increased aperiodic activity and EEG complexity, despite similar alpha power and clustering coefficient. The increased aperiodic activity aligns with findings in other comatose patients, including those sedated or with subcortical dysfunction. However, the increased entropy contradicts existing literature, suggesting that alpha-coma may represent a state of widespread cortical dysfunction likely resulting from nonhierarchical, turbulent brain activity. This indicates that the loss of consciousness does not guarantee consistent cortical measures across the whole spectrum of EEG patterns.

Key Words: Alpha-coma, Entropy, Coma, EEG, Aperiodic activity.

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EEG is a common measurement technique for clinical evaluation and prognostication in critically ill comatose patients. The degree of brain injury and dysfunction varies in coma and, in the most severe cases, can evolve into a persistent coma, vegetative state, or death.[1–3] Although coma is often considered a single entity, it is not. Coma may have different etiologies (brain injury or systemic dysfunction), and various mechanisms (structural, metabolic, toxic, etc.) and brain regions may be involved (cortical, subcortical).[4] This wide range of variables gives rise to various EEG patterns such as generalized periodic discharges, predominant delta background, suppression background, and epileptic activity among others.[5,6]

One such pattern is referred to as alpha-coma, a very rare and specific EEG pattern observed in comatose patients.[7] Kaplan et al.[8] described 36 patients with alpha-coma in a bicentric cohort study spanning over 10 years and added 335 other alpha-coma cases gathered from the literature since their original description.[9]

The alpha rhythm in alpha-coma patients typically ranges between 8 and 12 Hz and differs from the posterior distribution typically seen in healthy subjects; it has a widespread distribution

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The ethics committee approved the study (CE 2022-02046) in compliance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and waived patients' consent.

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often with frontal prominence and is usually nonreactive to various stimuli.[7] Despite the presence of an alpha rhythm, this pattern, if spontaneous and not due to medication or sedation effects, is almost invariably associated with poor prognosis. Predominantly occurring in post-cardiac arrest patients, alpha-coma may have other etiologies, such as pontomesencephalic and thalamic tumors, ischemic strokes, hemorrhages, and brainstem herniation,[8] which in turn may have different prognostic outcomes.

The rarity of alpha-coma makes it difficult to investigate its pathophysiology and EEG features. Alpha-coma is commonly believed to involve widespread cortical dysfunction, whereas the brainstem remains relatively preserved.[7,10]

The goal of the present study was to identify the distinctive electropathophysiological characteristics of the alpha-coma EEG pattern in a homogeneous group of comatose patients indexing the aperiodic component and the sample entropy of the EEG signal. The choice of these two biomarkers was made as they both have been associated with different level of consciousness in multiple studies[11–14] as well as theories,[15,16] but they have never been investigated on a cohort of comatose patients that match the predominant healthy cortical activity during wakefulness: the alpha wave.[17,18] We thus aimed to (1) characterize these components with respect to the posterior alpha rhythm seen in healthy subjects, (2) understand which measure is compatible (or not) with current theories and methodologies of consciousness, and (3) assess differences with other comatose patients in the aperiodic activity and temporal complexity found in the literature.

MATERIALS AND METHODS

Participants

Alpha-coma patients were retrospectively selected from medical charts at University Hospitals of Geneva, based on the following criteria: comatose patients[19] (FOUR[20] score <9), age >18 years, no intoxication, availability of a ≥ 19-channel EEG recording of at least 20 minutes performed during hospitalization, absence of sedation for more than 24 hours, ischemic or ischemic-hypoxic etiology, and clear patterns of alpha-coma as defined by Synek.[6] Glasgow Outcome Scale at discharge was collected. The ethics committee approved the study (CE 2022–02046) in compliance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and waived patient consent.

Healthy control subjects were retrospectively selected from an open-source database.[21] We performed age-controlled sampling to match the final sample size of the comatose population.

EEG Acquisition and Preprocessing

EEG recordings were acquired in the context of EEG evaluation in critical care patients using a 10 to 20 system EEG electrode placement (19 electrodes for all patients except for three patients that were recorded with 25 channels; 10–20 Deltamed and Micromed system [Natus] at 1000 Hz). A trained epileptologist and electrophysiologist (PDS) defined the alpha-coma state according to the standard criteria. The EEG of healthy volunteers was recorded with a BioSemi ActiveTwo system at 1000 Hz, using 64 electrodes following the positional scheme of the extended 10 to 20 system. Participants underwent 4 minutes of resting-state data collection while keeping their eyes closed.

Data were analyzed offline using MATLAB 2018 software (The Mathworks Inc). A bandpass Butterworth filter was used to filter the data between 1 and 30 Hz and a notch Butterworth filter was applied at 50 Hz. Data were then down-sampled to 250 Hz. Channels with poor signal-to-noise ratio were identified as those with a SD exceeding the first and third quartiles by a factor of two times the interquartile range (number of channels removed in controls $= 1 \pm 1.24$ and patients $= 0.35 \pm 74$). After removing these channels, an independent component analysis was performed to visually detect the components containing artifacts because of eyeblinks or heartbeats (number of components removed in controls $= 1 \pm 1$ and patients $= 3 \pm 2$). After, the noisy channels that were not included in the ICA were replaced by "spline" interpolation of the neighboring channels. Average rereferencing was then applied, and one epoch of 2 minutes was extracted for each participant. Finally, the base 19 scalp channels of the 10 to 20 system were selected to have homogeneous coverage across the two groups.

Power Spectra

We used Slepian sequences with multi-tapers to extract the power spectrum of the preprocessed 2 minutes of EEG data. The power spectrum was estimated for each channel in 5-second windows with a 50% overlap (Fig. 1A). We parameterized both the periodic and the aperiodic components by modelling the 1/f trend of the EEG power spectrum using the fitting oscillations & one over f algorithm.[22] This method iteratively fits log–log linear estimates (*aperiodic* activity) and multiple Gaussian curves (*periodic* spectral peaks) to determine the combination of parameters that better explain the variance of the cortical power spectrum. The fitting oscillations & one over f algorithm was implemented in Fieldtrip[23] using the following settings: default maximal number of peak set to 3, Gaussian peak width limited to 0.5 to 12 Hz, minimum peak height set to 3 dB, and fixed aperiodic mode, so no knee parameter was estimated. Frequency range was set to the lower band of the spectrum (2–20 Hz), as in previous studies.[12]

Next, the periodic component corresponding to the alpha range (8–12 Hz) was used to extract the five channels with the highest group-averaged alpha power within the same group of subjects (i.e., comatose patients and healthy control subjects; Fig. 1B). We used this approach to define a region of interest (ROI) that is not biased toward the known anteriorizations of alpha waves in comatose patients.[6] Sample entropy, the exponents of aperiodic activity (Fig. 1D), alpha power level, and average local clustering coefficient were then extracted from this ROI.

Power spectrum analysis and FOOF extraction were computed using the function "ft_freqanalysis" of the Fieldtrip toolbox.[23]

Sample Entropy

We used the sample entropy as a measure of the complexity of the EEG data to understand the predictability of the physiological signals of the two groups (Fig. 1C). Since the

focus of this work was the characterization of the alpha rhythm across healthy participants and alpha-coma patients, we restricted the analysis to the defined alpha-range (8–12 Hz). The preprocessed data series were band passed filtered between 8 and 12 Hz and then resampled to 48 Hz (details on the selection of the sampling frequency in **Supplemental Digital Content 1** (see Fig. S1, http://links.lww.com/JCNP/A306). Sample entropy is measured by examining the probability that two sequences of length $m+1$ will match based on the condition that they already match for the first m elements. A match is intended when the distance d between the two sequences is less than a certain tolerance r. The sample entropy is then practically estimated as negative logarithm of the ratio between the probability of matching sequences for $m+1$ and m. Thus, given our ROI time series with length $N = \{s_0, s_1, \cdots, s_N\}$, we can define a template vector i, $S_m(i) = \{s_i, s_{i+1}, \cdots, s_{i+m-1}\}$, and a sequence j, $S_m(j) = \{s_j, s_{j+1}, \cdots, s_{j+m-1}\}$, both with length m. The sample entropy of a specific channel for the 2-minute recordings was then computed as follows:

$$SampEnt = -\ln \frac{vectors\ with\ d(S_{m+1}(i), S_{m+1}(j)) < r}{vectors\ with\ d(S_m(i), S_m(j)) < r} \quad \forall\, j \neq i$$

where $d[\sim]$ is the Chebyshev distance between the two template vectors, the pattern length is set to $m = 2$, and the tolerance is set to $r = 0.5$. Finally, the sample entropy across all the channels within the ROIs was averaged.

Functional Connectivity and Clustering Coefficient

To further elucidate the electrophysiological correlates of the outcome of the sample entropy analysis, we conducted a post hoc connectivity analysis (Fig. 1E). The debiased weighted phase lag index was used to quantify the statistical dependencies between pairs of scalp signals in comatose patients and healthy subjects. This measure was chosen because, given that it depends purely on the phase difference between the pair of signals, it is unbiased toward the signal power. The debiased weighted phase lag index ranges between 0 and 1, where 0 indicates no coupling (or perfectly synchronous artifactual coupling) and 1 indicates perfect phase locking at a specific phase difference (different from 0 or π, which is assumed to be artifactual) (Vinck et al., 2011). It was calculated using the Fieldtrip toolbox, with the Fourier transform obtained using multitapers based on the Slepian sequence and a 2-Hz smoothing box. The resulting 3-dimensional array (19 × 19 × 321, where 19 is the number of EEG channels and 321 is the number of frequency bins spacing from 1 to 40 Hz) was averaged across the alpha range (8–12) Hz, yielding one functional connectivity (FC) matrix for each subject. The FC matrix was finally thresholded at 20% before computation of the ROI local clustering coefficient.

The FC matrix describes the brain as a network where the nodes are the different electrodes and the edges are their connections, reflecting the level of phase synchrony in the alpha range. To quantify the average level of synchrony in patients and

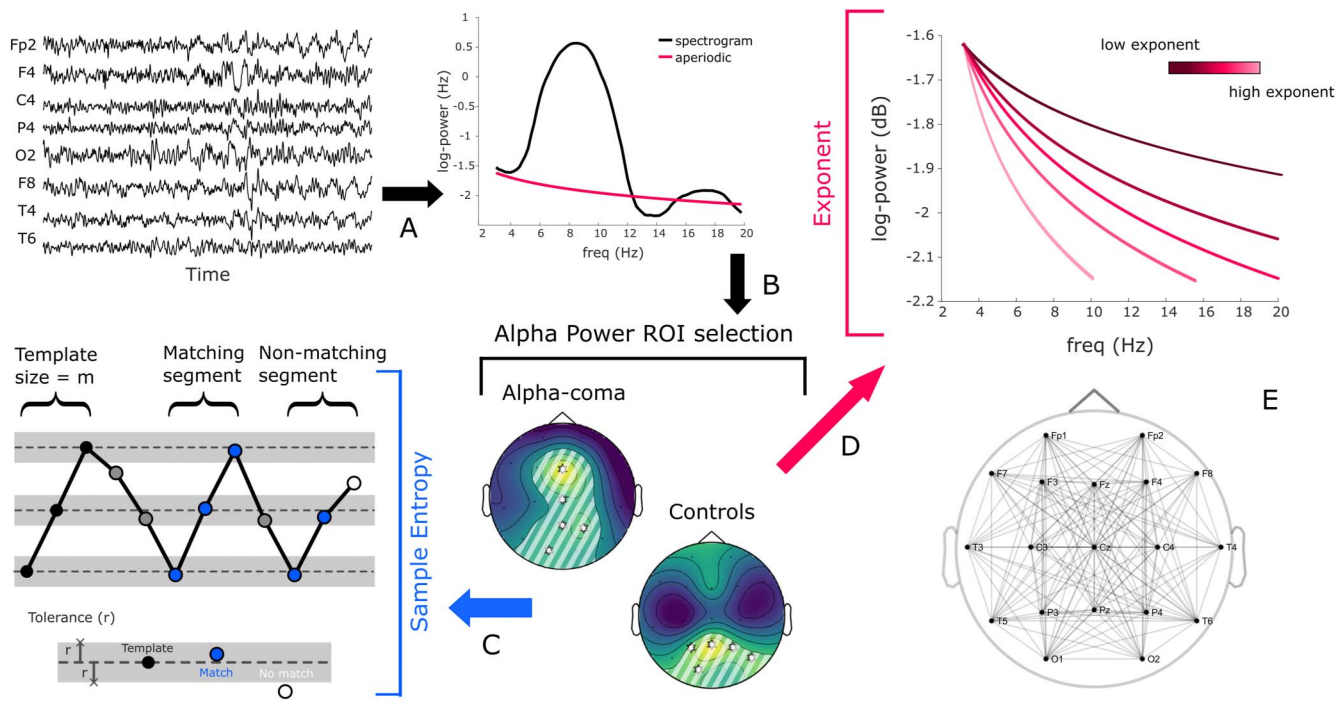

FIG. 1. Analysis pipeline of the current study. **A**, Frequency decomposition of the EEG time series was performed to extract the slope decay or aperiodic activity (red) from the spectrogram (black). **B**, Power spectrum analysis in the alpha band was conducted on the periodic part of the signal to identify the five best channels for each group. **C**, Sample entropy of each channel in the respective ROIs was calculated to assess the complexity of the alpha signal. **D**, Within each ROI, the spectral decay was averaged to compare changes in aperiodic activity across the two groups. **E**, Post hoc analysis of the functional connectome was also conducted. ROI, regions of interest.

control subjects and to relate it to EEG complexity, we extracted the clustering coefficient, defined as the sum of all its connections, and then averaged it across the nodes of the group-specific ROI.

Statistical Analysis

We used the Wilcoxon rank-sum statistic test to assess differences between the two groups in both alpha power levels, the exponents of the aperiodic activity, the sample entropy values, and the average network clustering coefficient. Additional logistic regression was computed to assess the discriminability of the two groups based on entropy levels while controlling for alpha power (glm package in R with binomial family[24]). Because of the exploratory nature of the analysis, Bonferroni correction was used to account for multiple comparisons across all tests. The adjusted *P*-values are reported in the Results section.

RESULTS

Among the 17 patients, 14 met the inclusion criteria (10 males; three were excluded due to poor data quality, history of drug abuse, and age). Twelve patients had cardiac arrest, whereas two had an ischemic stroke (one internal carotid occlusion, one basilar artery occlusion) (Table 1). Eleven patients died during their hospital stay (Table 1). EEG was performed within 1.58 ± 1.08 days from hospital admission.

We included 14 participants (7 men) from the total pool of 111 healthy participants. No difference in age was found between the two groups (alpha-coma group median age = 57 years, IQR = 15; healthy group median age = 58 years, IQR = 27; $p = 0.62$). Details of the sampling algorithm and selected IDs from the dataset can be found in the **Supplemental Digital Content 1** (see Fig. S2, http://links.lww.com/JCNP/A307).

Spectral Analysis

After fitting of the 1/f trend (healthy group: R^2 0.94 ± 0.04; alpha-coma group: R^2 0.95 ± 0.02, pVal = 0.42), we found no difference in alpha power between alpha-coma patients and healthy control subjects ($p = 0.11$; Cohen $d = 0.68$), we found a strong difference in the amount of aperiodic power ($p < 0.001$; Cohen $d = 2.12$) within these regions (Fig. 2).

Sample Entropy

We found that alpha-coma patients showed a greater complexity of the alpha-filtered EEG signal than the control group ($p = 0.002$; Cohen $d = 1.60$, Fig. 3A). Importantly, an additional orthogonalization of the sample entropy values against alpha power levels still showed a significant relationship between EEG complexity and the two groups (Beta logistic = 58.93, $p = 0.02$; Fig. 3B).

Post hoc Analysis of the Functional Connectome

We assessed whether the alpha FC of the group-specific ROIs played a role in the increased entropy observed in comatose patients (Fig. 3C). No significant difference was found in the local clustering coefficient of the respective group ROIs between alpha coma patients and healthy control subjects ($p = 0.89$; Cohen's $d = 0.29$; Fig. 3D), suggesting an uncorrelated relationship with EEG complexity.

DISCUSSION

In the present study, we investigated the neural EEG correlates of patients with alpha-coma compared with healthy control subjects with a normal alpha rhythm. Although no difference in alpha power was observed, patients with alpha-coma exhibited higher levels of aperiodic activity. Furthermore, sample entropy within the alpha range revealed a statistically significant increase in signal complexity in alpha-coma patients, with no differences in the functional connectome.

The nonoscillatory (aperiodic) part of the power spectrum, characterized by a scale-invariant slope decay (or 1/f), has been highlighted as an important and often neglected correlate of various cognitive, physiological, and behavioral phenomena.[22,25–30] Previous studies have demonstrated a correlation between the aperiodic component of neural activity and the excitatory-inhibitory balance,[31,32] with an increase in the slope exponent being associated with greater inhibition. Although this relationship does not always hold across computational models[33] and animal studies,[34] aperiodic activity has consistently been shown to reflect disruptions in conscious states.[11,12,29,35] In this framework, our findings showed an increase in exponent slope with a decrease of level of consciousness (i.e., alpha-coma vs. healthy participants) in agreement with previous work in human sleep,[26,29] anesthesia,[12] and disorder of consciousness.[11,35] Notably, recent research has shown that the decay of aperiodic activity remains consistent across various etiologies of coma[35] and even tracks different types of anesthesia,[12] with higher aperiodic exponents indicating deeper states and increased brain inhibition. Our results confirm a convergence toward a general inhibitory pattern in comatose patients compared with healthy

TABLE 1. Patient Clinical Details

ID	Age	Sex	Etiology	GOS at Discharge
01	66	M	CA	5
02	51	F	Stroke	3
03	60	M	Stroke	4
04	57	M	CA	5
05	54	M	CA	5
06	63	M	CA	4
07	24	F	CA	5
08	77	M	CA	3
09	81	M	CA	5
10	33	F	CA	5
11	50	M	CA	5
12	20	M	CA	5
13	85	M	CA	5
14	78	F	CA	5

M, male; F, female; CA, cardiac arrest; GOS, Glasgow Outcome Scale (unfavorable: scores ≥ 3).

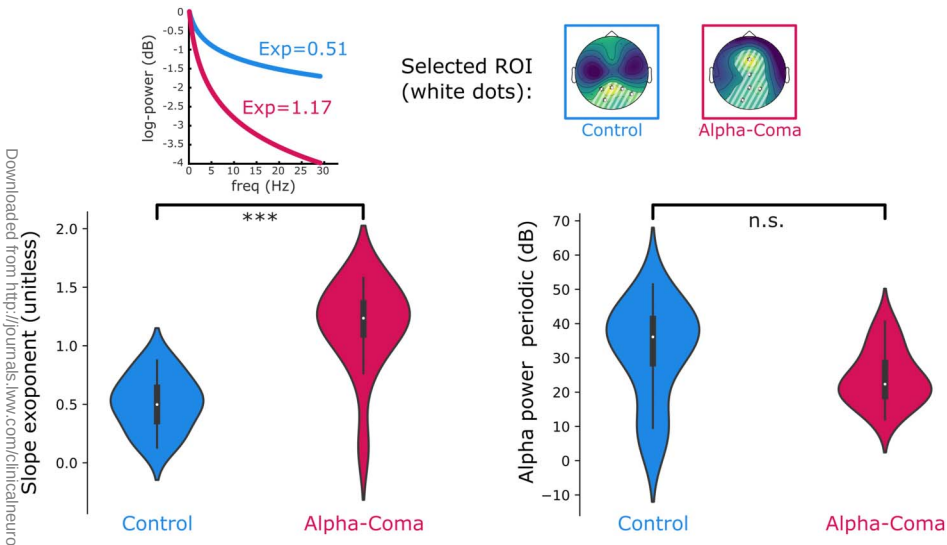

FIG. 2. Results of the spectral analysis. Average power and spectral decay within each ROI were computed for both groups. Although differences were observed in the slope of the spectrum between healthy participants and alpha-coma patients, no significant difference was found in alpha power levels. Top left of the figure: representation of the average aperiodic activity for each group. *** $p < 0.001$; n.s., not significant; ROI, regions of interest.

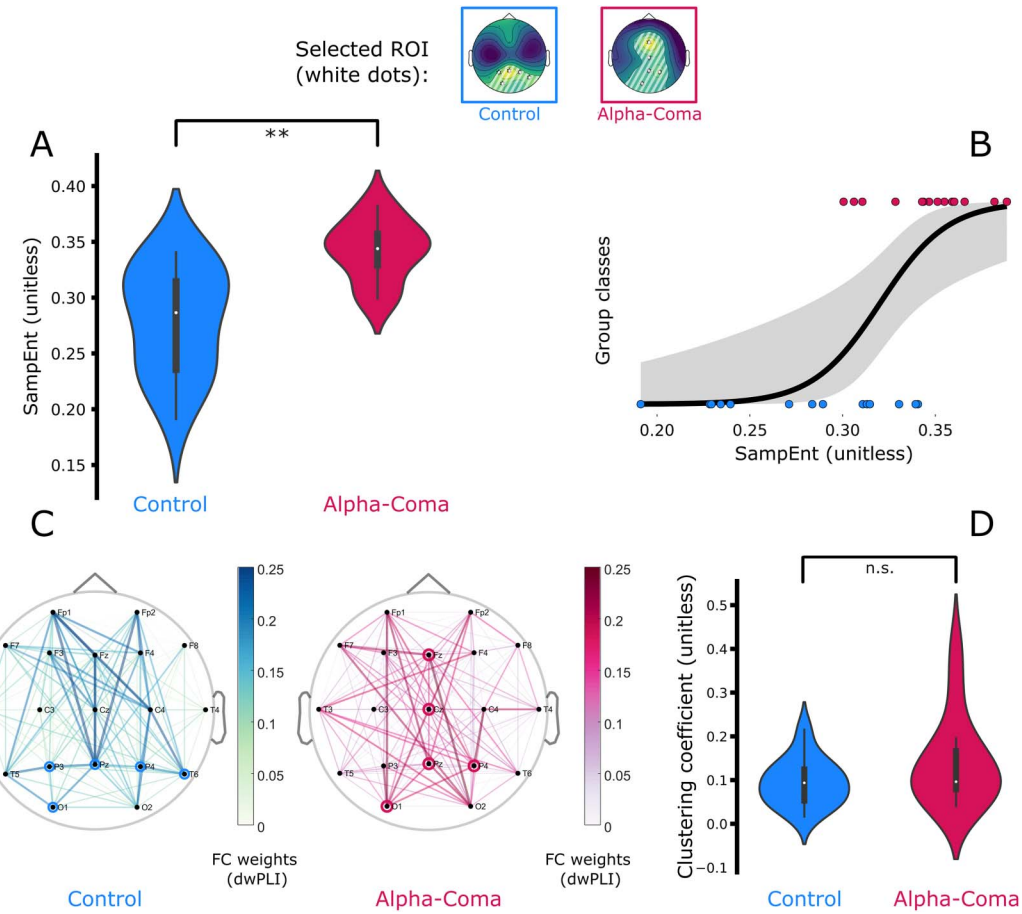

FIG. 3. Analysis of brain complexity. **A**, Significant differences in entropy levels were observed between alpha-coma patients and healthy participants within the alpha ROIs. **B**, Logistic regression demonstrated significant discrimination between the two classes based on entropy, even after controlling for alpha power levels. **C**, Average functional connectomes used for ROI clustering coefficient analyses. Colored circles are the ROI over which the functional connectivity metrics were computed. **D**, No significant differences were found in the ROI local clustering coefficient between the two groups. ** $p < 0.05$; n.s., not significant; ROI, regions of interest.

participants, even when controlling for matching alpha power levels.

Although our results on spectral decay are consistent with the current findings, the investigation of sample entropy in the alpha frequency band reveals an inverted effect. Sample entropy is a measure of the unpredictability of the EEG; when it is high, the signal has no clear pattern and its temporal evolution can be variable; when it is low, the signal tends to present a predictable pattern over time. Similar to aperiodic activity, changes in signal complexity have been found at different levels of unresponsiveness, such as during human sleep,[13,29,36–39] under varying degrees of anesthesia[14,40,41] and in disorders of consciousness,[42,43] suggesting that a decrease in sample entropy is usually associated with a state of generalized loss of information shared across the brain networks.[44] This evidence provides general support for the hypothesis that decreased brain complexity (and entropy) is often related to a loss of high-level cognitive abilities.[16,45,46]

Our analysis of the sample entropy revealed that alpha-coma patients may exhibit higher unpredictability and less regularity than healthy control subjects. The increase in entropy was unexpected, and post hoc connectivity analyses were conducted to further investigate this. Temporal entropy and spatial synchrony were found to be related in the context of disorders of consciousness, with higher entropy associated with higher levels of functional segregation.[15,47] Therefore, we tested whether the increased entropy in patients with alpha-coma was an indirect consequence of changes in functional connectivity. However, post hoc analysis showed that the increase in entropy in alpha-coma was not because of changes in functional connectivity because the clustering coefficient of the alpha ROI was the same across the two groups. Overall, our findings suggest that the entropy increase in alpha-coma patients is an epiphenomenon of autonomous rhythmicity that is highly variable because of its pathologic nature. This leads to the interpretation that the complexity of a cortical signal might be affected by a level of unpredictability that is unrelated to functional synchrony in the brain; instead, it is a mere reflection of the cortical noise of severe brain cortical dysfunction.

Early preclinical and clinical reports supported the hypothesis that alpha rhythm in alpha-coma is generated by mechanisms distinct from those responsible for the normal alpha background.[48,49] Previous findings have suggested that alpha-coma may represent a form of cortical auto-rhythmicity[50] arising from an anarchic cortical system disconnected from subcortical structures.[7,49]

Our results support the concept that the alpha rhythm in alpha-coma patients may reflect scalp EEG noise: in this specific scenario, raw EEG with a continuous and variable background should not be misinterpreted as a sign of potential recovery because it might present the scalp signature of an irreversibly damaged cortical system.

Despite the valuable insights provided by this study, several limitations of this study must be acknowledged. First, because of the rarity of the alpha-coma condition, the total sample size was relatively small, and there was a lack of homogeneity in etiology. Furthermore, because of poor clinical outcomes among patients with alpha-coma, there is insufficient variability in the sample to determine whether measures of brain complexity or aperiodic activity could serve as reliable predictors of clinical outcomes. The focus on the alpha frequency range also complicates direct comparisons with other comatose populations, where different EEG frequency ranges (e.g., alpha-theta, delta) might be more relevant. Nevertheless, based on our findings and what has been reported in the literature for selected populations of patients,[12,14,21,22] we propose a conceptual scheme that generates a new interpretation of these quantitative cortical measures (Fig. 4). Healthy wakeful subjects exhibit a balanced neuronal activity, whereas sedated and comatose patients display a predominant inhibitory pattern highlighted by an increase in the slope exponent of the power spectrum. In entropy, wakeful subjects show normal brain complexity, whereas comatose patients with primary subcortical dysfunction exhibit decreased entropy, similar to those under sedative agents. Conversely, comatose patients with primary cortical dysfunction, such as alpha-coma patients, demonstrate pathologically elevated levels of entropy, exceeding those of wakeful subjects, yet without correlation with cognitive function.

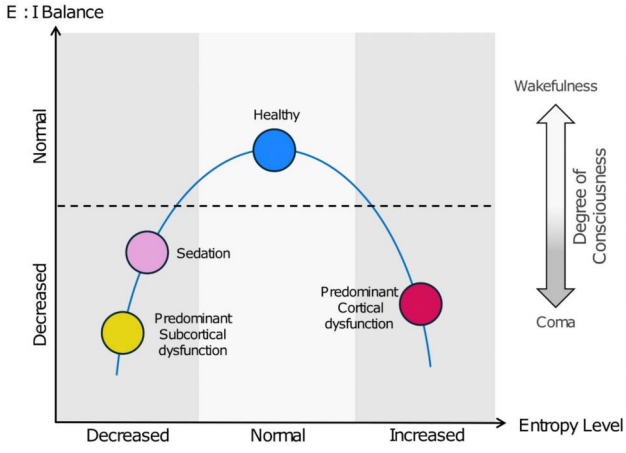

FIG. 4. Conceptual schematic representation of various states of consciousness in relation to excitatory-inhibition (E:I) balance and entropy level: Healthy, wakeful individuals exhibit a balanced E:I ratio and a normal level of entropy. Comatose patients show a reduced E:I balance: those under sedative agents and those with primary subcortical dysfunction exhibit decreased entropy. Comatose patients with primary cortical dysfunction, such as alpha-coma patients, demonstrate elevated levels of entropy.

CONCLUSIONS

Our results indicate that patients with alpha-coma exhibit EEG features of a predominant inhibitory pattern, similar to other disorders of consciousness. However, the entropy levels in patients with alpha-coma do not align with the expected behavior of a typical dysfunctional brain network. We propose that the use of entropy as a measure of overall cognitive-related brain complexity should be approached with caution, underscoring the importance of considering multiple measures when assessing level of consciousness.

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