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Aperiodic brain activity and response to anesthesia vary in disorders of consciousness

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ABSTRACT

In the human electroencephalogram (EEG), oscillatory power co-exist with non-oscillatory, aperiodic activity. Although EEG analysis has traditionally focused exclusively on oscillatory power, recent investigations have shown that the aperiodic EEG component can distinguish conscious wakefulness from sleep and anesthetic-induced unconsciousness. This study investigates the aperiodic EEG component of individuals in a disorder of consciousness (DOC); how it changes in response to exposure to anesthesia; and how it relates to the brain's information richness and criticality. High-density EEG was recorded from 43 individuals in a DOC, with 16 of these individuals undergoing a protocol of propofol anesthesia. The aperiodic component was defined by the spectral slope of the power spectral density. Our results demonstrate that the EEG aperiodic component is more informative about the participants' level of consciousness than the oscillatory component, especially for patients that suffered from a stroke. Importantly, the pharmacologically induced change in the spectral slope from 30 to 45 Hz positively correlated with individual's pre-anesthetic level of consciousness. The pharmacologically induced loss of information-richness and criticality was associated with individual's pre-anesthetic aperiodic component. During exposure to anesthesia, the aperiodic component distinguished individuals with DOC, according to their 3-month recovery status. The aperiodic EEG component has been historically neglected; this research highlights the necessity of considering this measure for the assessment of individuals in DOC and future research that seeks to understand the neurophysiological underpinnings of consciousness.

1. Introduction

Are there signatures in human brain activity that can be used to delineate an individual's state of consciousness? In the quest for electrophysiological markers of consciousness, the analysis of the human electroencephalogram (EEG) has traditionally been focused on oscillatory patterns within specific frequency bands, which are typically present as peaks in the power-spectral density (PSD). However, oscillatory peaks always co-occur with broadband non-oscillatory (i.e. aperiodic) activity, which can be described by the exponential (i.e. 1/f-like) decay of power over frequency (Donoghue et al., 2020, 2021). Recent advances in electrophysiology (Donoghue et al., 2020, 2021) suggest that

Abbreviations: CRS-R, Coma Recovery Scale-Revised; E/I, excitation/ inhibition; EOC, edge of chaos; PCF, pair correlation function; PSD, power-spectral density; UWS, Unresponsive Wakefulness syndrome; MCS, Minimally Conscious state; DOC, Disorders of consciousness; EEG, Electroencephalogram; LZC, Lempel-Ziv Complexity.

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analyzing EEG data solely from the perspective of oscillatory patterns may lead to erroneous or incomplete representations of the underlying neurophysiological processes.

Electroencephalography is a particularly promising tool for assessing the level of consciousness of individuals in a disorder of consciousness, as it is highly accessible in the clinical setting, has few patient contraindications and can be recorded at the bedside (Swisher and Sinha, 2016). Individuals in a disorder of consciousness following brain injury exhibit a wide range of reduced levels of awareness and arousal. As consciousness and responsiveness can be completely dissociated (Mashour and Avidan, 2013; Owen et al., 2006; Sanders et al., 2012), the identification of behavior-independent measures of consciousness is crucial for uncovering the mechanisms of human consciousness and improving clinical practice.

Although the PSD of healthy adult EEG is characterized by the presence of spectral peaks — predominantly in the theta and alpha bandwidth — the PSD of individuals in a disorder of consciousness often exhibits a total absence of such peaks (see Fig. 1A). Interpreting the remaining power of the aperiodic component erroneously as being oscillatory leads to several significant methodological problems (Donoghue et al., 2021). When not considered separately, putative changes in EEG oscillations across tasks and conditions might be underpinned entirely by alterations in the aperiodic component of the EEG. Thus, investigating the aperiodic component in the EEG of individuals

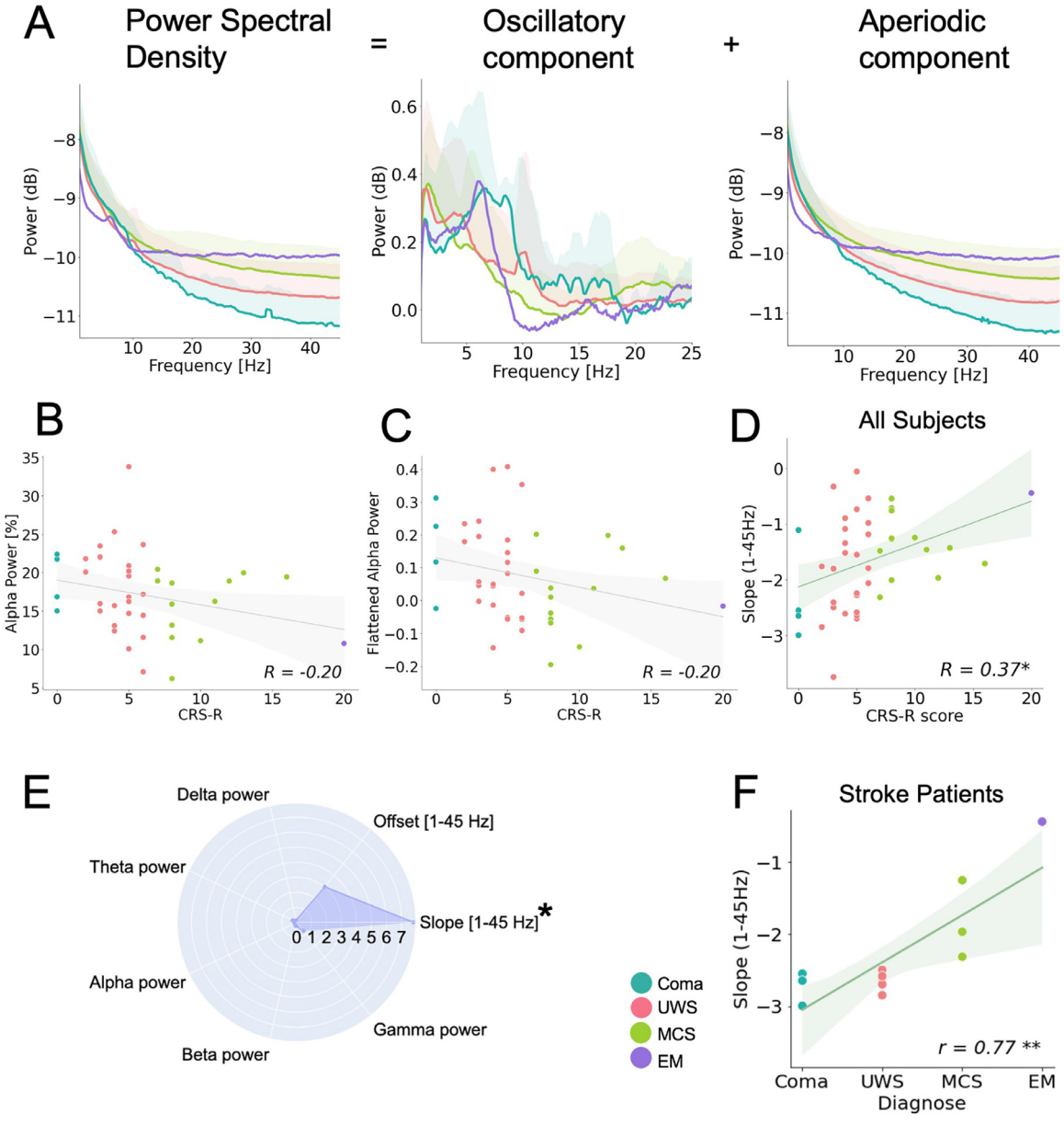

Fig. 1. Diagnostic value of EEG spectral properties in a disorder of consciousness. (A) The power spectral density of individuals in a disorder of consciousness (left) separates into an oscillatory component (middle) and an aperiodic component (right). (B) The traditional power analysis of oscillatory EEG in the alpha bandwidth does not predict individual's level of consciousness, as measured by the CRS-R score. (C) After removal of the aperiodic component, remaining oscillatory power of the EEG in the alpha bandwidth does not predict individuals' level of consciousness, as measured by the CRS-R score. (D) The aperiodic component of individuals EEG predicts individual level of consciousness, as measured by the CRS-R score. (E) Model coefficients after combining oscillatory and aperiodic features in multivariate linear regression model. Only the aperiodic slope is a significant predictor for individuals' level of consciousness. For the purpose of visualization (B-D), R scores were obtained through univariate linear regressions. (F) The aperiodic component of the EEG predicts level of consciousness only in stroke patients. * indicates $p < 0.05$, ** indicates $p < 0.01$. UWS: Unresponsive Wakefulness Syndrome, MCS: Minimally Conscious state, EM: Emergence.

in disorders of consciousness might also lead to more complete representations of the neurophysiological underpinnings of consciousness.

Recent studies have shown that the properties of the aperiodic EEG contain information about consciousness, which are neglected in traditional oscillation-based analyses (Colombo et al., 2019; Colombo et al., 2023; Lendner et al., 2020). States of unconsciousness, such as non-rapid eye movement sleep (Lendner et al., 2020) and anesthetic-induced unconsciousness (Colombo et al., 2019; Lendner et al., 2020) exhibit a steeper spectral slope (i.e., a faster power decay over frequencies), compared to wakefulness. Changes in the aperiodic EEG were further observed after exposure to psychoactive drugs (Muthukumaraswamy and Liley, 2018; Timmermann et al., 2019) and in a variety of pathological neurologic and psychiatric conditions (Pani et al., 2022). As such, the aperiodic component has been widely proposed as an electrophysiological marker for the assessment of individuals in a disorder of consciousness (Colombo et al., 2019; Lendner et al., 2020).

During conscious wakefulness, the brain has been widely suggested to operate close to criticality — a point of optimal computational capacity and information-richness where the underlying network is poised between order and disorder (Beggs and Plenz, 2003; Carhart-Harris, 2018; Carhart-Harris et al., 2014; O'Byrne and Jerbi, 2022; Toker et al., 2022; Zimmern, 2020). This balance is putatively maintained by a proper tuning between excitation and inhibition (E/I) (Shew et al., 2011; Zhou and Yu, 2018). The aperiodic EEG and has been linked to the local E/I balance, the brain's information-richness and criticality (Gao et al., 2017; Medel et al., 2020; Muthukumaraswamy and Liley, 2018; Toker et al., 2022). Being additionally correlated to established consciousness metrics, such as the Perturbation Complexity Index (Casali et al., 2013; Colombo et al., 2019), the aperiodic component has shown much promise for the investigation of mechanisms underlying consciousness, especially in individuals who are behaviorally unresponsive.

Using EEG recorded under various conditions of pharmacologically and pathologically induced unconsciousness, this study aims to characterize the aperiodic component associated with consciousness for individuals in a disorder of consciousness, and in particular, how this component changes in response to exposure to anesthesia and how it relates to altered network complexity and criticality. General anesthesia is known to reliably reduce levels of consciousness *and* responsiveness by globally perturbing brain networks underlying consciousness (Purdon et al., 2013). Investigating the anesthetic-induced change of the aperiodic component in individuals in a disorder of consciousness provides a unique perspective on mechanisms underlying human consciousness. We first hypothesized that the aperiodic EEG component would have diagnostic value for individuals in a disorder of consciousness above and beyond the traditional analysis of EEG oscillatory power. We further hypothesized that the pharmacologically induced change in the aperiodic component would vary with individuals' level of, and capacity for, consciousness, and that this change would be accompanied by the brain's loss of network criticality.

2. Materials and methods

2.1. Participants and anesthetic protocol

This study combined two existing datasets of participants in a disorder of consciousness (i.e., one dataset of baseline EEG recordings and one dataset of individuals in a DOC, undergoing an anesthetic protocol). In total, 43 individuals in a disorder of consciousness and coma (22 male, 42 ± 15.13 years old) were included in this study. Individuals in a disorder of consciousness were included following acquired brain injury (18 anoxic, 12 traumatic brain injury, 12 stroke) and assessed by a trained experimenter using the Coma Recovery Scale-Revised (CRS-R) (Kalmar and Giacino, 2005) (see Supplementary Table 1). Participants were excluded if they were receiving sedation at the time of the study. For all participants, written informed consent was provided by their legal representative in accordance with the Declaration of Helsinki. The study was approved by the McGill University Health Center Research Ethics Board (15-996-MP-CUSM) and the Western University Health Science Research Ethics Board (Project ID 100628). Among the participants a disorder of consciousness, 14 were in MCS, 25 in UWS and four in a coma (CRS-$R = 5.88 \pm 4.02$). For participants in an acute disorder of consciousness ($n = 18$), clinical outcomes were assessed three months post-recording. At this time, six participants had recovered full consciousness (i.e., were able to respond verbally and consistently follow commands). Eleven participants did not recover consciousness and remained in a disorder of consciousness. One participant had life-sustaining treatment withdrawn and was excluded from the analysis of prognostic value (see Supplementary Table 1).

Sixteen of the above described individuals in a disorder of consciousness (5 male, 44 ± 18.24 years old) underwent an anesthetic protocol, explained in Blain-Moraes et al. (2016). Briefly, participants were anesthetised with propofol at a target effect site concentration of 2.0 μg/ml. In this study, we include a period of 5 min resting state prior to the start of the anesthetic protocol (referred to as: Baseline state) as well as the period of 5 min during the infusion of propofol, after the effect site concentration of 2.0 μg/ml has been reached (referred to as: Anesthetized state). Within this subset ($n = 16$), 11 individuals were in an acute state. Within three months post-recording, five participants had recovered full consciousness (i.e., were able to respond verbally and consistently follow commands), five participants did not recover consciousness and one participants had life-sustaining treatment withdrawn (see Supplementary Table 1).

2.2. Electroencephalography data

EEG in both datasets was recorded from a 128-channel EGI Sensor Net using an Amps 400 amplifier (Electrical Geodesic, Inc., USA), a sampling rate of 1 kHz and vertex reference. Electrode impedance was reduced to below 5KΩ prior to data collection. Two EEGs were recorded using a 64-channel EEG system. Prior to analysis, the raw signal was filtered between 0.5 and 55 Hz, average referenced and resampled to 250 Hz. A notch filter was applied at 60 Hz. Channels with an excessive level of noise were removed prior to average referencing. Non-brain channels were removed from the subsequent analysis. The signal was then segmented in non-overlapping epochs of 10 s. The signal was visually inspected by a trained investigator to manually reject epochs containing nonphysiologically artifacts. All preprocessing steps were performed using the MNE python toolbox (Gramfort et al., 2013).

2.3. Spectral slope and power analysis

The power spectra were calculated for every electrode and epoch, using the Multitaper approach (Prerau et al., 2017). All spectral estimates were performed using a frequency range from 0.5 to 50 Hz and a frequency smoothing of ±0.5 Hz, resulting in the use of 9 discrete prolate slepian sequences (dpss) tapers (Prerau et al., 2017). The aperiodic component was defined by the EEG spectral slope and offset which were calculated using the FOOOF package (Donoghue et al., 2020). This algorithm parametrizes the EEG into an aperiodic and oscillatory component. The aperiodic component of the PSD over frequencies F is defined by:

$$Aperiodic\ component = b - \log(k + F^{\chi}),$$

where b is the spectral offset, k is the knee parameter and χ is the spectral slope. To be coherent with previous research (Colombo et al., 2019; Lendner et al., 2020), the spectral slope was defined by $-\chi$. To capture the aperiodic component of the traditionally assessed bandwidths, we focused on the spectral slope in the 1–45 Hz. Due to prior evidence that the spectral slope in higher frequencies (> 30 Hz) is specifically sensitive on the effect of anesthesia (Colombo et al., 2019; Lendner et al., 2020), we also assessed the spectral slope in the 30–45 Hz range. In the

1–45 Hz range, the algorithm was fit using the fixed and knee aperiodic mode (min_*peak_height* = 0.1, max_*n_peaks* = 10). Whereas the knee mode fits an additional parameter k to the data, this parameter is set to 0 in the fixed mode. In the 30–45 Hz range we exclusively used the fixed mode to fit the data. This can be justified by the narrower frequency band which does not require a knee fit. The results from the model using the knee mode yield an overall better model fit (see Supplementary Fig. 1) and was presented in this paper. The model error and analysis using the knee mode is provided in the supplementary material (see Supplementary Fig. 1). Following the methods from Lendner et al. (2020), the power spectra, as well as the spectral slope were calculated for every participant, epoch, and electrode independently and averaged subsequently. Is it notable that estimating the aperiodic component on the time-averaged PSD did not affect any of the results.

Power analysis in the delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (30–45 Hz) bands was performed before and after the removal of the broadband aperiodic component from the PSD. In the first part, oscillatory power was calculated using the relative contribution of one frequency band to the overall PSD. In the second step, the PSD was flattened (i.e., the aperiodic component was removed) using the FOOOF package (Donoghue et al., 2020). The resulting oscillatory power was averaged within each frequency band. To identify whether the PSD of a signal participant exhibits a peak frequency, a separate model was fit on the electrode-averaged PSD. The propofol-induced change of the aperiodic component Δslope and Δoffset was defined as the difference between the baseline value and the value in the anesthetized state (Baseline − Anesthesia). Due to strong artefacts above 30 Hz, two subjects were excluded from the analysis of the spectral slope in the 30–45 Hz range.

2.4. Complexity and criticality

Signal information-richness was calculated using four measures of Lempel-Ziv complexity (LZC). All estimates of LZC were calculated on every epoch individually and averaged subsequently. For all estimates of LZC, the signal was low pass filtered at 45 Hz and binarized using the mean of its instantaneous amplitude. For the univariate LZC, complexity was calculated on every channel individually and averaged subsequently, using the median over all channels in one epoch (Lempel and Ziv, 1976). For the concatenated LZC, the signal of all channels in one epoch was concatenated before compression, as described by Schartner et al. (2015).

To account for biases of the spectral properties on the signal complexity, both measures of LZC were normalized using two approaches (1) shuffle-normalization and (2) phase-normalization. In the first approach the LZC of every epoch is normalized by the complexity of the randomly shuffled binarized time-series (Schartner et al., 2015). The second method compares the signal's LZC to a phase-randomized surrogate of this signal and has been demonstrated to be most robust against spectral changes of the signal (Toker et al., 2022). Both estimates of LZC were calculated using the code provided by Toker et al. (2022) and an additional custom function for shuffle-normalization.

Criticality of the brain network was defined using the pair correlation function (PCF), which is an estimate of global phase synchronization or network susceptibility (Kim and Lee, 2019; Lee et al., 2018; Yoon et al., 2015). Due to its previously demonstrated link to levels of consciousness and the information integration of the underlying brain network (Kim and Lee, 2019; Lee et al., 2018), we estimated the PCF in the 8–13 Hz range. The PCF was estimated for every epoch individually and averaged subsequently.

To provide a second measure of network criticality, we further estimated the network's closeness to the edge of chaos (EOC). Chaoticity was estimated using the modified 0–1 chaos test (Gottwald and Melbourne, 2004; Toker et al., 2022). Following the recommendations of Toker et al. (2022), signal chaoticity was estimated on the low-frequency cortical activity. We therefore applied the FOOOF algorithm on every channel and epoch individually to identify the highest peak frequency between 1 and 6 Hz. Channels without an oscillatory peak in this frequency range were removed from chaoticity analysis (this was the case for 22.90% of the signal, see Discussion). The edge of chaos criticality was estimated using the methods provided by Toker et al. (2022) and the proposed alpha of 0.85 (see Discussion). The propofol-induced change in both measures was defined as the difference between the baseline value to the value in the anesthetized state.

2.5. Statistical analysis

Statistical analysis was performed using Python Pingouin (Vallat, 2018). In the first section, the link between the oscillatory and aperiodic component with participants' CRS-R score was assessed using a multivariate linear regression. Assumptions were tested using Shapiro-Wilk test. Reported R and R^2 values correspond to the *adjusted* values. For visualization only, individual R and R^2 were obtained using univariate linear regression. Confidence intervals were estimated using bootstrapping (1000 iterations). Correlation with subjects' diagnosis was performed using the spearman rank correlation.

In the second part, the change of the spectral slope, criticality, complexity and chaoticity in response to propofol anesthesia was assessed using repeated measures *t*-test. P-values were corrected using Bonferroni-correction. Effect size was calculated using Cohens d. The correlation between Δslope and individual's CRS-R score was estimated using spearman rank test. The effect between the spectral slope at baseline and its propofol-induced change was assessed using Pearson correlation. Group differences between recovered and non-recovered participants were assessed using independent *t*-test. All p-values were corrected using Bonferroni-correction. To control for known changes of the aperiodic component over lifespan (Voytek et al., 2015), all models were controlled for participants' age.

3. Results

3.1. Aperiodic EEG component contains more diagnostic value than oscillatory power for individuals in a disorder of consciousness

The spectral slope was the only significant predictor of participants' CRS-R score (see Table 1) and explained 12% of the variance ($R^2 = 0.12$, $F(1,40) = 6.67$, $p < 0.05$) (see Fig. 1D). Individuals with higher levels of consciousness exhibited a flatter slope (see Fig. 1A). In contrast to previous research (Chennu et al., 2014; Lechinger et al., 2013), we did not find a significant relation between spectral power in any frequency band and participants' CRS-R score (see Fig. 1B, Supplementary Fig. 1 for all frequency bands). The oscillatory-only component (i.e., after removal of the aperiodic component) was not predictive of an individual's CRS-R score (see Fig. 1C, Supplementary Fig. 1 for all frequency bands).

Table 1
Linear model with combined band-limited power and aperiodic features.

Coefficients						
					95% CI	
	b	SE	t	p	Lower	Upper
(Intercept)	46.4634	70.975	0.655	0.517	−97.776	190.703
Age	−0.0496	0.038	−1.301	0.202	−0.127	0.028
Slope [1–45 Hz]	7.7759	2.595	2.997	0.005	2.503	13.049
Offset [1–45 Hz]	3.0198	1.72	1.756	0.088	−0.475	6.514
Power Delta	−0.14	0.591	−0.237	0.814	−1.34	1.06
Power Theta	0.2933	0.563	0.521	0.606	−0.851	1.437
Power Alpha	−0.1542	0.602	−0.256	0.799	−1.378	1.069
Power Beta	0.2467	0.688	0.359	0.722	−1.152	1.645
Power Gamma	−0.7381	2.838	−0.26	0.796	−6.507	5.03

Note: Null model contained Age, SE: Standard Error.

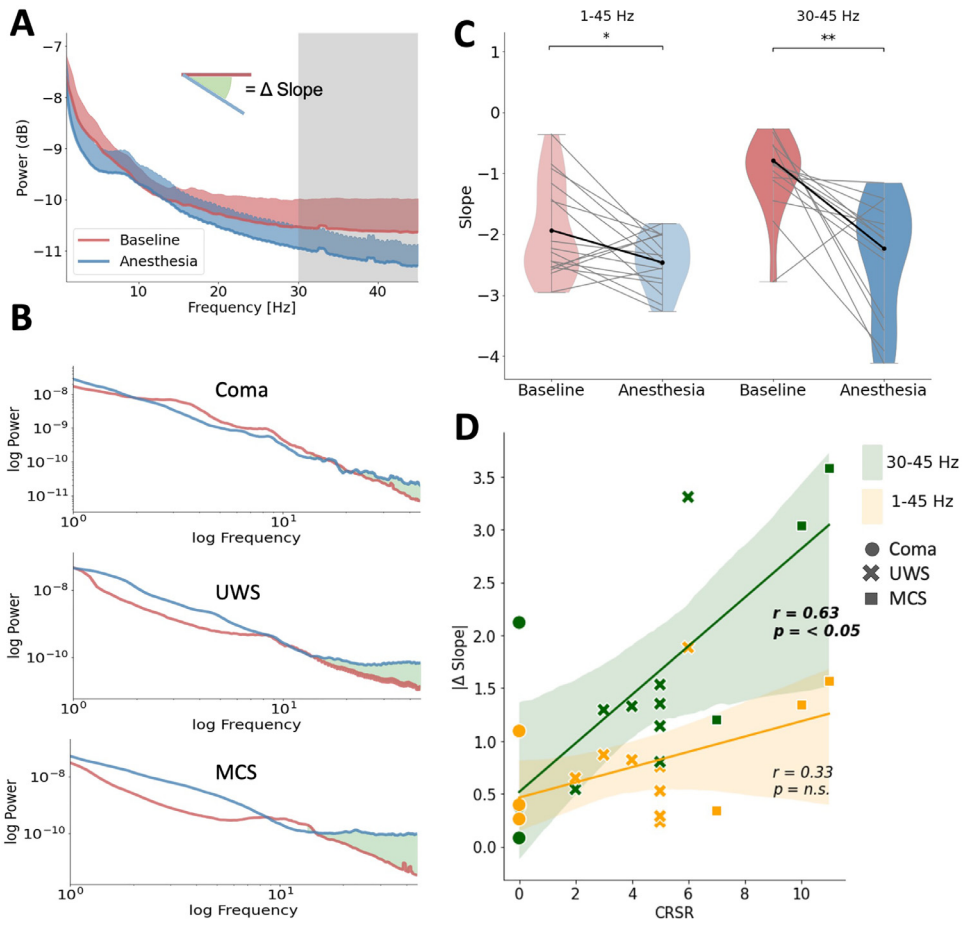

Fig. 2. Alterations of the spectral slope in a disorder of consciousness and general anesthesia. (A) Power spectral density of Baseline (red) and Anesthesia state (blue), averaged across participants. (B) Power spectral density of Baseline (red) and Anesthesia state (blue) in a log-log scale, averaged across participants in a coma (top) in a Unresponsive Wakefulness Syndrome (middle) and a Minimally Conscious state (bottom). The green area denotes the anesthetic-induced change of the spectral slope in the higher frequency range. (C) Change in spectral slope in response to propofol anesthesia in 1–45 Hz (left) and 30–45 Hz (right). (D) The absolute change in spectral slope over all channels in the 30–45 Hz range correlates with participants' CRS-R score. * indicates $p < 0.05$, ** indicates $p < 0.01$. UWS: Unresponsive Wakefulness Syndrome, MCS: Minimally Conscious state.

An oscillatory peak could be identified in only 13 out of 43 individuals in a DOC (see Supplementary Fig. 2). Peaks were predominantly identified in the theta to lower-alpha frequency range (5.1 Hz ± 3.01). Neither the peak frequency, nor the power of the identified peak oscillation (for $n = 13$) correlated with individuals' CRS-R score (see Supplementary Fig. 2, see Discussion). Most importantly, no oscillatory peak was detected in the remaining 30 participants, leaving solely the aperiodic EEG component for analysis.

A post-hoc analysis on patient's etiology revealed a significant correlation between patients' diagnosis (i.e., coma, UWS, MCS, EM) and the spectral slope only in stroke patients ($r(9) = 0.77$, $p < 0.01$), but not in patients who suffered an anoxic or traumatic brain injury (see Fig. 1F, Supplementary Fig. 3 for all etiologies).

There was no significant correlation between the offset of the aperiodic component and participants' CRS-R score. The spectral slope was significantly steeper in acute disorders of consciousness, compared to individuals with chronic disorders of consciousness ($t(41) = 2.63, p < 0.05$, $d = 0.80$) (see Supplementary Fig. 1). There was no significant difference in the spectral slope or the identified peak between participants who did or did not recover consciousness three months following EEG assessment. All results were replicated using the 'fixed mode' of the FOOOF algorithm (see Supplementary Fig. 1).

3.2. Participants with higher levels of consciousness exhibit larger changes of the aperiodic EEG component in response to anesthesia

Anesthesia significantly steepened the spectral slope in the 30–45 Hz range ($t(13) = 3.80$, $p < 0.01$, $d = 1.64$) and the 1–45 Hz range ($t(15) = 2.542$, $p < 0.05$, $d = 0.83$) (see Fig. 2A, 2C). The Δslope in both frequency ranges was dependent on the spectral slope at Baseline, with a flatter spectral slope at Baseline indicating a stronger change in response to propofol (see Supplementary Fig. 4). Most interestingly, the absolute amount of Δslope (i.e. | Δslope|) in the 30–45 Hz range predicted participant's CRS-R score ($r(12) = 0.63$, $p < 0.05$), with a higher CRS-R score indicating a stronger change of the aperiodic component in response to propofol (see Fig. 2B,D). At difference with the previously shown anesthetic-induced steepening of the spectral slope (Colombo et al., 2019; Lendner et al., 2020), some participants exhibited a flattening of the spectral slope in response to exposure to anesthesia in the 1-45 as well as the 30-45 Hz range (see Fig. 2C, see Discussion). However, the correlation to individual's level of consciousness was also present when considering the directionality of change ($r(12) = 0.48$, $p < 0.05$) (i.e. without taking the absolute value). In both cases, participants with a higher CRS-R score exhibited a larger steepening of the spectral slope in response to propofol anesthesia. This effect could not be replicated in the 1–45 Hz range (see. Fig. 2D). While the Δslope in the 30–45 Hz range was homogenously distributed, the slope in the 1–45 Hz range differed between central-parietal and lateral regions (see Supplementary Fig. 4). Participants' Δslope did not differ between chronic and acute states (see Supplementary Fig. 4). All results were replicated using the spectral offset (see Supplementary Fig. 5).

3.3. Propofol-induced loss of chaoticity and information-richness relies on pre-anesthetic EEG spectral slope

Anesthesia had no significant group-level effect on any estimate of signal complexity (i.e. concatenated phase-normalized, concatenated shuffle-normalized, univariate phase-normalized, univariate shuffle-normalized) (see Supplementary Fig. 6). Similarly, no significant group-level effect was observed in signal chaoticity, the PCF, and the closeness to the EOC (see Supplementary Fig. 6). Instead, individuals in a disorder of consciousness exhibited a heterogenous set of reactions in response

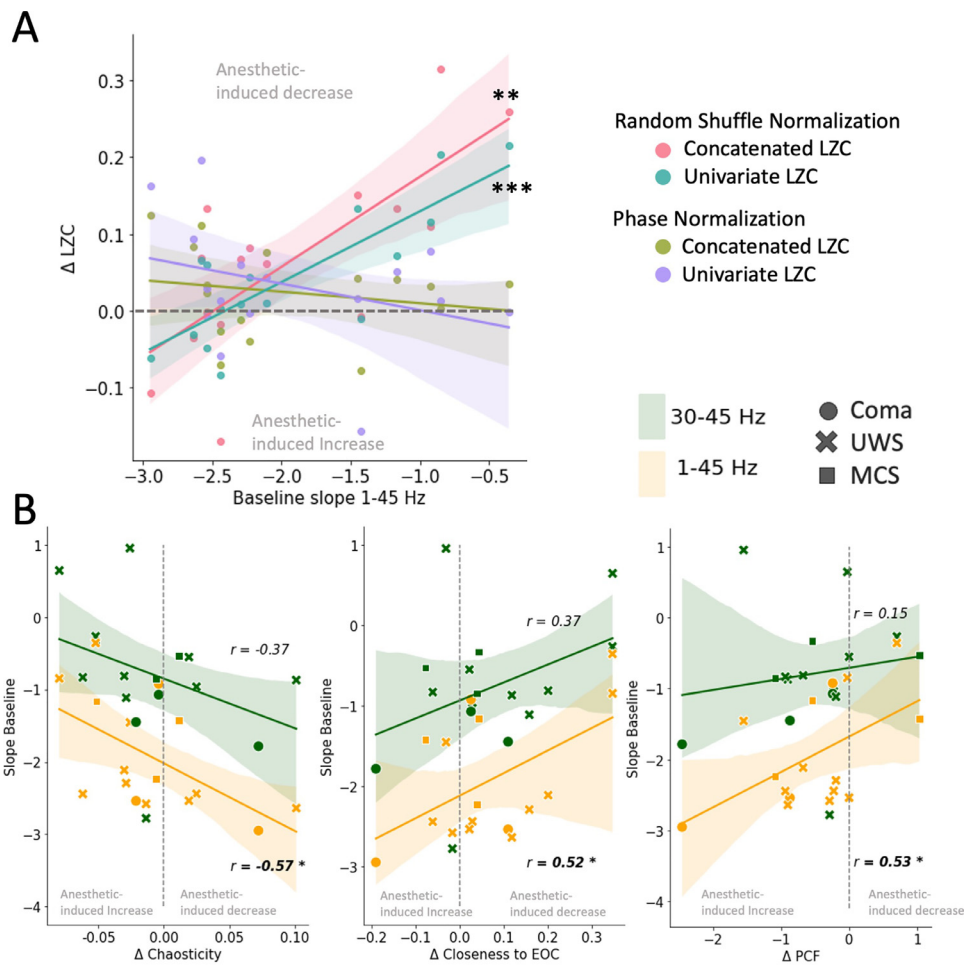

Fig. 3. Relation between the spectral slope at baseline and the anesthetic-induced change of (A) signal complexity, using four different types of LZC, and (B) Chaoticity, Closeness to edge of chaos (EOC) and the pair correlation function (PCF). * indicates $p < 0.05$, ** indicates $p < 0.01$, *** indicates $p < 0.001$. UWS: Unresponsive Wakefulness Syndrome, MCS: Minimally Conscious state.

to propofol anesthesia (see Supplementary Fig. 6). In contrast with previous research in healthy adults (Kim and Lee, 2019; Toker et al., 2022), some participants exhibited an increase in PCF and complexity, decrease in chaoticity and approach to the EOC under exposure to propofol anesthesia.

We assessed how the anesthetic-induced change of the signal complexity, chaoticity and criticality depended on the brain's spectral slope in the Baseline state. In the 1–45 Hz range, the spectral slope at Baseline correlated positively with the anesthetic-induced change of the PCF ($r = 0.53$, $p < 0.05$), closeness to EOC ($r = 0.52$, $p < 0.05$), the shuffle-normalized concatenated LZC ($r = 0.74$, $p < 0.01$) and shuffle-normalized univariate LZC ($r = 0.81$, $p < 0.001$) (see Fig. 3). The spectral slope in the 1–45 Hz range at Baseline correlated negatively with signal chaoticity ($r = -0.57$, $p < 0.05$). No correlation was observed with the spectral slope in the 30–45 Hz range. Cumulatively, a flatter spectral slope at Baseline resulted in a stronger decrease of the PCF, stronger distancing from EOC, stronger loss of complexity (i.e., using shuffle-normalized LZC) and stronger increase in chaoticity under exposure to propofol anesthesia. Using the phase-normalization for LZC (i.e., to reduce the bias of spectral changes), the relation to the spectral slope at Baseline neutralized (see Fig. 3A), indicating that the shown effects in signal complexity are highly biased by spectral changes of the signal (see Discussion).

Additionally, we demonstrated how the anesthetic-induced change of the signal complexity, chaoticity and criticality is not only dependent on the properties of the brain at Baseline but is also reflected in the anesthetic-induced change of the spectral slope. The propofol-induced change of the spectral slope in the 1–45 Hz range correlated positively with the change of the PCF ($r = 0.56$, $p < 0.05$) and negatively with the change of the chaoticity ($r = -0.58$, $p < 0.05$) (see Supplementary Fig. 7). No significant correlation was observed between the change of the spectral slope and the change of the closeness to the EOC (see Supplementary Fig. 7). The change in the spectral slope in the 1–45 Hz range correlated positively with shuffle-normalized concatenated ($r = 0.56$, $p < 0.05$) and univariate LZC ($r = 0.60$, $p < 0.05$), but negatively with phase-normalized concatenated ($r = -0.51$, $p < 0.05$) and univariate LZC ($r = 0.57$, $p < 0.05$) (see Discussion). Cumulatively, a stronger steepening of the spectral slope in response to propofol anesthesia was accompanied by a stronger loss of signal complexity (i.e., as estimated by shuffle-normalized LZC), criticality (as estimated by decreased PCF) and stronger increase of chaoticity. Surprisingly, the measures of LZC, which were argued to be less biased by the spectral properties of the signal (i.e., using phase-normalization) inversed this relation with a stronger steepening of the spectral slope indicating a stronger information gain (see Discussion).

3.4. The aperiodic EEG component and concatenated complexity during exposure to anesthesia contains prognostic information for individuals in a disorder of consciousness

During the anesthetized state, the 1–45 Hz aperiodic EEG component distinguished participants who recovered consciousness three months post-EEG from those who did not recover consciousness (see Fig. 4A). Participants who recovered consciousness exhibited a significantly steeper spectral slope ($t(8) = 3.14$, $p < 0.05$, $d = -1.99$), compared to participants who did not recover consciousness (see Figure 4A). At a group-level, there was no prognostic value in the spectral slope at Baseline, nor in the propofol-induced change of the aperiodic component (see Fig. 4B). However, a post-hoc analysis on patient's etiology revealed a significant prognostic value of the propofol-induced change

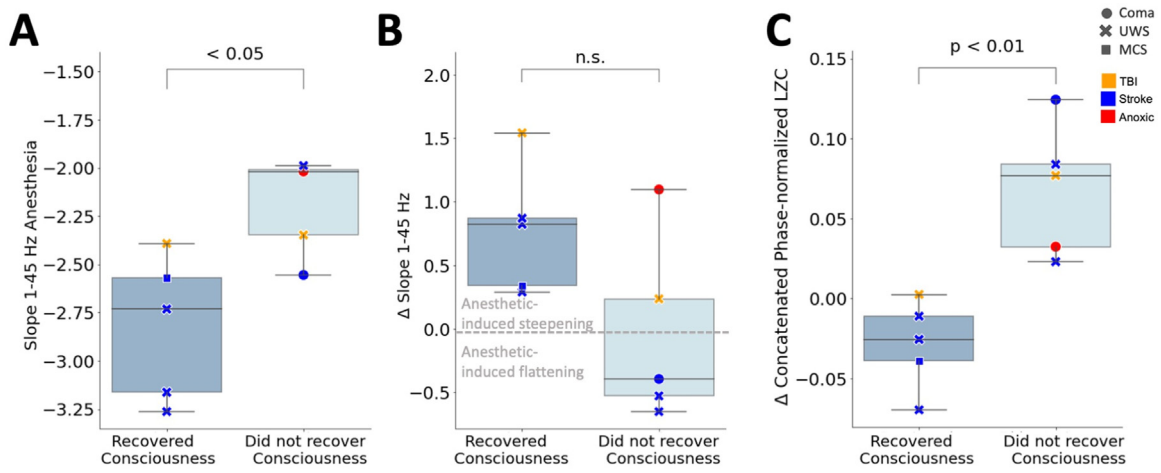

Fig. 4. Prognostic value of the spectral slope and signal complexity (A) The spectral slope during anesthesia in the 1–45 Hz range differs between individuals who did and did not recover consciousness three months post-EEG. (B) The anesthetic-induced change of the spectral slope does not contain prognostic information for disorders of consciousness. (C) The anesthetic-induced change of the concatenated LZC contains prognostic information for disorders of consciousness. Error bars represent standard errors. UWS: Unresponsive Wakefulness Syndrome, MCS: Minimally Conscious state, TBI: Traumatic brain injury.

of the aperiodic component for stroke patients. Whereas patients who recovered consciousness within three months post-recording showed the expected anesthetic-induced steepening in the aperiodic component, non-recovered stroke patients showed the opposite effect ($t(8) = 5.73$, $p < 0.01$, $d = 4.37$). Due to the small sample size of patients who suffered an anoxic or traumatic brain injury, prognostic value could not be assessed for those etiologies individually. No prognostic value was found in the 30–45 Hz range.

Due to the lack of group-level prognostic value in the propofol-induced steepening of the spectral slope, we performed a *post hoc* analysis investigating the prognostic value in the change of LZC. Most interestingly, this analysis revealed prognostic value in the propofol-induced change of the LZC (see Fig. 4C). While participants who later recovered consciousness exhibited a propofol-induced increase of phase-normalized concatenated LZC, the signal complexity of participants who did not later recover consciousness decreased in response to anesthesia ($t(8) = -4.35$, $p < 0.01$, $d = -2.75$) (see Discussion). A significant group difference was also present using phase-normalized univariate LZC ($t(8) = -2.55$, $p > 0.05$, $d = -1.61$). Whereas none of the complexity measures showed prognostic value at Baseline, the univariate ($t(8) = 3.00$, $p < 0.05$, $d = 1.89$) and concatenated ($t(8) = 2.40$, $p < 0.05$, $d = 1.51$) phase-normalized complexity during the exposure to propofol were significantly higher in patients who recovered consciousness. For both presented effects, prognostic value of LZC was only present when using shuffle normalization and disappeared when using phase normalization.

4. Discussion

This is the first study to investigate the aperiodic component of EEG and its response to propofol for the assessment of level of and capacity for consciousness in individuals in a DOC. We showed that the aperiodic component in the baseline EEG of individuals in a DOC contains diagnostic information above and beyond traditional analysis of periodic EEG components, especially for stroke patients. The significance of this finding is underscored by the fact that although 70% of the participants in a disorder of consciousness included in this study did not have an EEG oscillatory peak, analysis of EEG oscillatory power remains by far the most prevalent method for investigating the brain activity in this population. Building upon previous work from our group showing that global brain network perturbation using anesthesia has prognostic value (Duclos et al., 2022), we also investigated the diagnostic and prognostic value of the aperiodic EEG component change upon exposure to propofol. We showed that the propofol-induced change of the EEG aperiodic component positively correlated with individual's pre-anesthetic level of consciousness, with higher levels of consciousness indicating a larger propofol-induced steepening of the spectral slope. We further showed that the pharmacologically induced change of the spectral slope, information-richness and criticality relied on individual's pre-anesthetic aperiodic component. During exposure to anesthesia, the aperiodic component and brain complexity contained prognostic value for individuals with a DOC. The diagnostic and prognostic effect was strongest for patients who suffered from a stroke. Cumulatively, our results highlight the urgent need to reconsider analysis brain activity in DOC in light of the diagnostic and prognostic information contained in the traditionally discarded aperiodic EEG component.

It has been widely proposed that the diagnostic and prognostic power of the EEG aperiodic component should be investigated in brain-injured, unresponsive patients (Colombo et al., 2019; Lendner et al., 2020). The strong evidence that the aperiodic EEG component distinguishes states of wakefulness from sleep (Lendner et al., 2020) and general anesthesia (Colombo et al., 2019; Lendner et al., 2020) motivated investigations of diagnostic value of this signal for unresponsive patients. In a clinical population, Lanzone et al. (2022) proposed the aperiodic slope as an index for longitudinal recovery from stroke. Colombo et al. (2023) demonstrated the value of the aperiodic component beyond alpha power as a marker of pharmacological- and pathologically induced unconsciousness. Further, Alnes et al. (2021) assessed the spectral properties of pathologically unresponsive individuals and showed that the aperiodic component of the EEG is altered in patients in a coma, compared to healthy adults.However, EEG in this study was recorded when participants were under varying levels of sedation: this critically affects interpretation of the results, as the non-oscillatory characteristics of disorders of consciousness are overshadowed by the known effect of anesthesia on the spectral slope. Our study compares the aperiodic EEG component for participants in a DOC before and during exposure to a targeted and stable concentration of anesthesia, not only dissociating these two potentially confounding factors, but also illustrating the diagnostic potential of the within-subject changes in spectral slope in this population.

Traditionally, DOC have been described through alterations in the power of canonical EEG frequency bands (Bai et al., 2017). Recent best practice in EEG analysis recommends removing the aperiodic component from the signal prior to power analysis (Donoghue et al., 2021). However, the EEG of individuals in a DOC is most commonly characterized by a total absence of oscillatory peaks. While this prevents any meaningful oscillation-based analysis, our study demonstrated that the

aperiodic component of EEG still contains important information about the individual's level and capacity for consciousness. However, the results of our study do not support neglecting oscillatory power per se; rather, they highlight the value of the aperiodic component in populations where oscillatory peaks are not systematically present.

Although previous research found significant correlations between participants' CRS-R score and power in alpha (Chennu et al., 2014) and delta bandwidths (Lechinger et al., 2013), we did not reproduce these results in the current study. We consider three possible explanations for this discrepancy: first, whereas Chennu et al. (2014) included individuals with a CRS-R score above 7, only 24% of the participants in the present study met this criterion. This suggests that EEG oscillations may increase nonlinearly with an individuals' level of consciousness, which should be explored in future research. Second, when analyzing power in narrow frequency bands, changes in the power spectrum driven solely by the slope of the aperiodic component can be misinterpreted as a decrease in low frequencies and increase in high frequencies (Donoghue et al., 2021). Thus, the previously shown increased delta power in individuals with lower levels of consciousness (Chennu et al., 2014; Lechinger et al., 2013) might in fact be epiphenomenal to a steepening of the spectral slope, instead of oscillatory power. Third, 43% of study participants suffered an anoxic injury. While patients in a DOC are often characterized by a peak in the theta or low alpha frequency, the total absence of spectral peaks (i.e. type A of 'ABCD' model) has been linked to complete loss of thalamocortical integrity (Forgacs et al., 2017). Whereas traumatic brain injury and stroke are typically focal injury which affect a single or a group of regions, anoxic injury has a more global impact and is thus more likely to lead to a complete loss of thalamocortical integrity. Thus, the lack of diagnostic value in the oscillatory component in this study could be attributed to the high proportion of participants with severe anoxic brain injury. In line with this, Colombo et al. (2023) described reduced alpha power as not being an index of unconsciousness, but rather a marker of overall cortical suppression, which is most prevalent in anoxic brain injury.

Other studies have also presented evidence for the role of EEG oscillatory power in the assessment of disorders of consciousness. Lechinger et al. (2013) demonstrated a correlation between the occipital peak frequency and individuals' level of consciousness. However, participants who did not exhibit an oscillatory peak were excluded from the analysis (Lechinger et al., 2013). We hypothesize that oscillatory power and peak frequency, if present, can play a complementary role to the aperiodic component for the diagnosis of levels of consciousness. Although we cannot test this hypothesis directly in this study, as only six out of 43 participants exhibited an oscillatory peak in the 4–13 Hz range, this remains a fruitful area for further research. In the case that no oscillatory peak is present, our results demonstrate that the diagnostic value of EEG for individuals in a DOC might be fully attributable to the aperiodic component.

Despite strong evidence that the spectral slope is related to consciousness (Colombo et al., 2019, 2023; Lendner et al., 2020), there is disagreement about whether it is a measure of arousal (i.e., vigilance (Lendner et al., 2020) or of consciousness level (i.e., awareness) (Colombo et al., 2019). Rather than framing our results within these dimensions – which have been criticized as failing to represent the multifaceted nature of consciousness and its disorders (Bayne et al., 2016) — we focus on a mechanistic interpretation of the aperiodic component and its link to consciousness. Using *in silico* modeling, the slope of the aperiodic component has been suggested to be a marker of the network's E/I balance (Gao et al., 2017; Medel et al., 2020). Moreover, consciousness has been proposed to be underpinned by an optimal E/I balance (Toker et al., 2022), which tunes the brain towards a state of criticality and information-richness (Shew et al., 2011). When this balance is disrupted (i.e., more inhibition than excitation) the network diverges from criticality, exhibits a steeper spectral slope (Gao et al., 2017; Medel et al., 2020; Zimmern, 2020) and reduced signal complexity (Medel et al., 2020). Our results further support the proposition that the brain of individuals in a DOC operates far from a critical point (Toker et al., 2022), resulting in weaker network susceptibility to global perturbations, such as propofol anesthesia.

Exposure to the inhibitory drug propofol causes steepening of the spectral slope (Colombo et al., 2019; Lendner et al., 2020), reflecting the brain's shift towards inhibition. In this study, the anesthetic-induced change of the spectral slope correlated with participants' CRS-R score and thus, depended on their baseline level of consciousness. One potential explanation for this phenomenon is that the effect of propofol depends on the pre-anesthetic E/I balance. While exposure to propofol has a large effect on a well-balanced brain, an imbalanced brain may have a reduced capacity to shift, as it is closer to a floor-level of maximum imbalance. In other words, the already-steepened spectral slope in comatose patients could reflect the brain's high imbalance and distance from criticality, resulting in a reduced response to propofol anesthesia. Comparably, stronger brain network reconfiguration in the alpha bandwidth following exposure to propofol has been linked to higher potential for recovery of consciousness (Duclos et al., 2022). Thus, one potential interpretation of our results is that individuals in a disorder of consciousness are characterized by an E/I imbalance, with higher imbalance resulting in a reduced reaction of the aperiodic component to general anesthesia and lower levels of consciousness.

Despite the group-level steepening of the spectral slope during exposure to anesthesia, some individuals in a DOC exhibited an alternative pattern: a flatter spectral slope in the anesthesia state, accompanied by a more complex signal and increased criticality. Toker et al. (2022) observed a similar inconsistency, with one individual in a DOC exhibiting increased chaoticity after regaining consciousness. Similarly, one subject described by Lendner et al. (2020) exhibited an anesthetic-induced flattening of the 1–40 Hz spectral slope. Although an increase of complexity and flattening of the spectral slope following exposure to anesthesia is counterintuitive for healthy individuals, disorders of consciousness might be a heterogenous set of conditions, which might derive from criticality either towards a subcritical or a supercritical state (i.e., be either too chaotic or too stable). In a previous study from our group, we demonstrated paradoxical increase of consciousness-related markers (i.e., brain complexity and frontoparietal connectivity) in a case series of three DOC patients after administration of propofol (Maschke et al., 2022). The spectral slope in the 1–45 Hz range at baseline clearly separated individuals with a disorder of consciousness into two groups: individuals with flatter slopes exhibited a propofol-induced steepening of the slope, while individuals with slopes steeper than 2.6 showed a countertrend flattening of the spectral slope (see Fig. 2C). Although counterintuitive, the results recapitulate the arousing effect of zolpidem (a GABAergic drug) on patients in a DOC (Du et al., 2014; Machado et al., 2014; Noormandi et al., 2017; Sripad et al., 2020). We postulate that GABAergic drugs might alter their inhibitory function similarly to the GABAshift in postnatal development (Peerboom and Wierenga, 2021) to be advantageous for over-inhibited brains. Further characterization of the clinical differences between these groups and the effect of propofol is warranted in future research.

Pharmacologically induced reduction of signal complexity has been previously demonstrated in numerous studies on healthy individuals using propofol, isoflurane and sevoflurane (Hudetz et al., 2016; Schartner et al., 2015; Toker et al., 2022; Wang et al., 2017; Zhang et al., 2001). However, in this study, we could not identify a group-level decrease of LZC. In contrast, we demonstrated that the loss of signal complexity was strongly related to the signal's spectral properties prior to exposure to anesthesia and in response to anesthesia. Whereas the relation between the spectral slope and signal complexity has been previously shown using modeling studies (Medel et al., 2020), this study provides the first evidence from a clinical population. Most interestingly, the relation between the spectral slope and the signal complexity vanished or inversed after normalizing the LZC with phase-randomized surrogate, which was argued to be most robust to spectral changes of the signal (Toker et al., 2022). This suggests that observed changes of LZC

- which are commonly normalized using signal length or a randomly shuffled signal - might be largely driven by spectral changes after exposure to anesthesia. An independent investigation of anesthetic-induced loss of signal complexity and change of the aperiodic component for the evaluation of levels of consciousness would be recommended for future research.

The results of this study should be interpreted in light of several limitations. First, participants were assessed using the JFK Coma Recovery Scale-Revised (Kalmar and Giacino, 2005), which is a behavioral scale for the assessment of responsiveness. The resulting score is widely used as a surrogate measure of consciousness. However in a DOC, consciousness can be fully dissociated from behavior (Mashour and Avidan, 2013; Owen et al., 2006; Sanders et al., 2012). Thus, it is possible that the true level of consciousness in study participants was not accurately captured by this metric and that true levels of consciousness were underestimated by the behavioral score of responsiveness. Whereas the first part of this study (Baseline recording) cannot differentiate whether the aperiodic component captures levels of consciousness or responsiveness, the value of the aperiodic component for detecting covert consciousness in unresponsive individuals could be explored in future research. In the second part of this study, participants in a DOC underwent a protocol of propofol anesthesia. Independent of the pre-anesthetic level of responsiveness, the individual's anesthetic-induced brain reaction and changes in the spectral slope are attributable to loss of consciousness, which might diverge from the degree of anesthetic-induced loss of responsiveness. Thus, a strong brain reaction to anesthetics despite low to no behavioral changes, might be an indicator for higher pre-anesthetic levels of consciousness reaching beyond the estimated level of responsiveness. This possibility should be more closely investigated in future research. Additionally, the trend towards low CRS-R score within this study's participants led to high imbalance between the classical diagnostic groups (i.e., coma, unresponsive wakefulness syndrome, minimally conscious state, emergence). We therefore did not perform a group-comparative statistical analysis to distinguish the classical diagnostic categories.

Second, participants in this study were recruited after a variety of brain injuries, including stroke, traumatic and anoxic brain injury. While the diagnostic value was most strongly expressed in patients who suffered from a stroke, the identified prognostic value relies on an extremely small sample size and did not allow conclusions about traumatic and anoxic brain injury. Whereas the spectral slope has been shown to be steeper in the hemisphere most affected by a stroke (Lanzone et al., 2022), this study did not account for the location of the brain injury. In line with previous research by Alnes et al. (2021) who did not identify diagnostic value of the spectral slope in patients following anoxic brain injury, and Lanzone et al. (2022), our study supports the diagnostic and prognostic value of the spectral slope of stroke patients.

Third, whereas the diagnostic value of the spectral slope during the baseline state was present in the 1–45 Hz range, the anesthetic-induced change of the spectral slope in this frequency range was not significantly correlated with patient's pre-anesthetic level of consciousness. Only the change of the aperiodic component in higher frequencies (30–45 Hz) significantly increased with higher pre-anesthetic levels of consciousness. While this frequency range has been previously shown to be particularly sensitive to propofol-induced loss of consciousness (Lendner et al., 2020), it is also known to be most strongly contaminated by electromyography (EMG) artifacts. As we did not record EMG in this study, we cannot exclude the possibility that the EMG influences the spectral slope in the 30–45 Frequency range. However, the change of the spectral slope in both frequency ranges was dependent on the spectral slope in 1–45 Hz at Baseline, with a flatter spectral slope at Baseline indicating a stronger change in response to propofol (see Supplementary Fig. 4).

Fourth, this study explored the link between the aperiodic component and network criticality, measured by the PCF (Kim and Lee, 2019) and the modified 01-chaos test (Toker et al., 2022). The PCF specifically in the alpha frequency range has shown a strong link to measures of consciousness (Kim and Lee, 2019; Lee et al., 2018). Despite the lack of an alpha peak the PCF in this study was estimated in the 8–13 Hz range. An influence of increased alpha-power during exposure to propofol on the estimate of PCF cannot be excluded. Following the provided methods by Toker et al. (2022) the modified 0–1 chaos test was only performed on channels which exhibited an oscillatory peak in the 1–6 Hz range. There is a large variety of measures within the methodological framework of network criticality (O'Byrne and Jerbi, 2022; Zimmern, 2020); the broader exploration of the aperiodic component and its relation to different measures of criticality, which do not rely on oscillation, is strongly recommended for future research. For the estimation of the closeness to EOC, we used an alpha of 0.85, as proposed by Toker et al. (2022). This value has been empirically defined to distinguish levels of wakefulness from unconscious states. A validation or refinement of this value in a larger clinical population would be recommended in further research. Fourth, the detection of oscillatory peaks in the first part of the analysis was performed on the electrode-averaged spectrum. Previous research has demonstrated the value of the alpha postero-anterior gradient for the assesment of consciousness (Colombo et al., 2023). Whereas most individual's electrode-averaged PSD did not exhibit oscillatory peaks, we cannot exclude the possibility of oscillatory peaks on the level of single electrodes and did not investigate the value of the spatial distribution of alpha power.

5. Conclusion

We demonstrate the value of the aperiodic EEG component for the assessment of individuals in a disorder of consciousness following brain injury. At Baseline, individuals with a lower level of consciousness exhibit a steeper spectral slope (i.e., faster decay of power over frequency). The anesthetic-induced change in the aperiodic component depends on individual's pre-anesthetic level of consciousness and accompanies the brain's loss of criticality. The aperiodic EEG component has been historically discarded; this research highlights a critical need to reconsider the traditional treatment of this component of the EEG in research with individuals in a disorder of consciousness.

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Ethics statement

For all participants, written informed consent was provided by their legal representative in accordance with the Declaration of Helsinki. The study was approved by the McGill University Health Center Research Ethics Board (15-996-MP-CUSM) and the Western University Health Science Research Ethics Board (Project ID 100628).

Data and code availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request and the instantiation of a formal data sharing agreement between all implicated institutions. The code used for this paper is available on Github: https://github.com/

BIAPT/Aperiodic_EEG. The version of all used packages is specified in the requirements.

Declaration of Competing Interest

The authors report no competing interests.

Credit authorship contribution statement

Charlotte Maschke: Conceptualization, Methodology, Formal analysis, Software, Writing – original draft, Visualization. **Catherine Duclos:** Writing – review & editing, Investigation. **Adrian M. Owen:** Writing – review & editing, Project administration, Resources. **Karim Jerbi:** Writing – review & editing, Project administration, Supervision. **Stefanie Blain-Moraes:** Funding acquisition, Writing – review & editing, Investigation, Project administration, Supervision.

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Supplementary materials

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References

Alnes, S.L., Lucia, M.D., Rossetti, A.O., Tzovara, A., 2021. Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma. Neuroimage 245, 118638.

Bai, Y., Xia, X., Li, X., 2017. A review of resting-state electroencephalography analysis in disorders of consciousness. Front. Neurol. 8. doi:10.3389/Ffneur.2017.00471.

Bayne, T., Hohwy, J., Owen, A.M., 2016. Are there levels of consciousness? Trends Cogn. Sci. 20 (6), 405–413.

Beggs, J.M., Plenz, D., 2003. Neuronal avalanches in neocortical circuits. J. Neurosc. 23 (35), 11167–11177.

Blain-Moraes, S., Boshra, R., Ma, H.K., Mah, R., Ruiter, K., Avidan, M., … Mashour, G.A., 2016. Normal brain response to propofol in advance of recovery from unresponsive wakefulness syndrome. Front. Hum. Neurosci. 10, 10.

Carhart-Harris, R.L., 2018. The entropic brain - revisited. Neuropharmacology 142, 167–178.

Carhart-Harris, Robin Lester, Leech, R., Hellyer, P.J., Shanahan, M., Feilding, A., Tagliazucchi, E., … Nutt, D., 2014. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front. Hum. Neurosci. 8.

Casali, A.G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K.R., … Massimini, M., 2013. A theoretically based index of consciousness independent of sensory processing and behavior. Sci. Transl. Med. 5 (198), 198ra105 -198ra105.

Chennu, S., Finoia, P., Kamau, E., Allanson, J., Williams, G.B., Monti, M.M., … Bekinschtein, T.A., 2014. Spectral signatures of reorganised brain networks in disorders of consciousness. PLoS Comput. Biol. 10 (10), e1003887.

Colombo, M. A., Comanducci, A., Casarotto, S., Derchi, C.-C., Annen, J., Viganò, A., … Rosanova, M., 2023. Beyond alpha power: EEG spatial and spectral gradients robustly stratify disorders of consciousness. Cerebral Cortex bhad031.

Colombo, M.A., Napolitani, M., Boly, M., Gosseries, O., Casarotto, S., Rosanova, M., … Sarasso, S., 2019. The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. Neuroimage 189, 631–644.

Donoghue, T., Haller, M., Peterson, E.J., Varma, P., Sebastian, P., Gao, R., … Voytek, B., 2020. Parameterizing neural power spectra into periodic and aperiodic components. Nat. Neurosci. 23 (12), 1655–1665.

Donoghue, T., Schaworonkow, N., Voytek, B., 2021. Methodological considerations for studying neural oscillations. Eur. J. Neurosc. 55, 1–26.

Du, B., Shan, A., Zhang, Y., Zhong, X., Chen, D., Cai, K., 2014. Zolpidem arouses patients in vegetative state after brain injury: quantitative evaluation and indications. Am. J. Med. Sci. 347 (3), 178–182.

Duclos, C., Maschke, C., Mahdid, Y., Nadin, D., Rokos, A., Arbour, C., … Blain-Moraes, S., 2022. Brain responses to propofol in advance of recovery from coma and disorders of consciousness: a preliminary study. Am. J. Respir. Crit. Care Med. 205 (2), 171–182.

Forgacs, P.B., Frey, H., Velazquez, A., Thompson, S., Brodie, D., Moitra, V., … Claassen, J., 2017. Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury after cardiac arrest. Ann. Clin. Transl. Neurol. 4 (2), 119–129.

Gao, R., Peterson, E.J., Voytek, B., 2017. Inferring synaptic excitation/inhibition balance from field potentials. Neuroimage 158, 70–78.

Gottwald, G.A., Melbourne, I., 2004. A new test for chaos in deterministic systems. Proc. R. Soc. Lond. Ser. A Math. Phys. Eng. Sci. 460 (2042), 603–611.

Gramfort, A., Luessi, M., Larson, E., Engemann, D., Strohmeier, D., Brodbeck, C., … Hämäläinen, M., 2013. MEG and EEG data analysis with MNE-Python. Front. Neurosci. 7. Retrieved from https://www.frontiersin.org/article/10.3389/fnins.2013.00267 .

Hudetz, A.G., Liu, X., Pillay, S., Boly, M., Tononi, G., 2016. Propofol anesthesia reduces Lempel-Ziv complexity of spontaneous brain activity in rats. Neurosci. Lett. 628, 132–135.

Kalmar, K., Giacino, J.T., 2005. The JFK coma recovery scale—Revised. Neuropsychol. Rehabil. 15 (3–4), 454–460.

Kim, H., Lee, U., 2019. Criticality as a determinant of integrated information Φ in human brain networks. Entropy 21 (10), 981.

Lanzone, J., Colombo, M.A., Sarasso, S., Zappasodi, F., Rosanova, M., Massimini, M., … Assenza, G., 2022. EEG spectral exponent as a synthetic index for the longitudinal assessment of stroke recovery. Clin. Neurophysiol. 137, 92–101.

Lechinger, J., Bothe, K., Pichler, G., Michitsch, G., Donis, J., Klimesch, W., Schabus, M., 2013. CRS-R score in disorders of consciousness is strongly related to spectral EEG at rest. J. Neurol. 260 (9), 2348–2356.

Lee, U., Kim, M., Lee, K., Kaplan, C.M., Clauw, D.J., Kim, S., … Harris, R.E., 2018. Functional brain network mechanism of hypersensitivity in chronic pain. Sci. Rep. 8 (1), 243.

Lempel, A., Ziv, J., 1976. On the complexity of finite sequences. IEEE Trans. Inf. Theory 22 (1), 75–81.

Lendner, J.D., Helfrich, R.F., Mander, B.A., Romundstad, L., Lin, J.J., Walker, M.P., Knight, R.T., 2020. An electrophysiological marker of arousal level in humans. eLife 9, e55092.

Machado, C., Estevez, M., Rodriguez, R., Perez-Nellar, J., Chinchilla, M., DeFina, P., … Perez-Cruz, N., 2014. Zolpidem arousing effect in persistent vegetative state patients: autonomic, EEG and behavioral assessment. Curr. Pharm. Des. 20 (26), 4185–4202.

Maschke, C., Duclos, C., Blain-Moraes, S., 2022. Paradoxical markers of conscious levels: effects of propofol on patients in disorders of consciousness. Front. Hum. Neurosci. 16. Retrieved from https://www.frontiersin.org/articles/10.3389/fnhum.2022.992649 .

Mashour, G.A., Avidan, M.S., 2013. Capturing covert consciousness. Lancet 381 (9863), 271–272.

Medel, V., Irani, M., Ossandón, T., & Boncompte, G. (2020). *Complexity and 1/f slope jointly reflect cortical states across different E/I balances* (p. 2020.09.15.298497). 10.1101/2020.09.15.298497

Muthukumaraswamy, S.D., Liley, D.T.J, 2018. 1/f electrophysiological spectra in resting and drug-induced states can be explained by the dynamics of multiple oscillatory relaxation processes. Neuroimage 179, 582–595.

Noormandi, A., Shahrokhi, M., Khalili, H., 2017. Potential benefits of zolpidem in disorders of consciousness. Expert Rev. Clin. Pharmacol. 10 (9), 983–992.

O'Byrne, J., Jerbi, K., 2022. How critical is brain criticality? Trends Neurosci. 45 (11), 820–837.

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., Pickard, J.D., 2006. Detecting awareness in the vegetative state. Science 313 (5792), 1402 –1402.

Pani, S.M., .Saba, L., & Fraschini, M. (2022, June 15). Clinical applications of EEG power spectra aperiodic component analysis: a mini-review. PsyArXiv.

Peerboom, C., Wierenga, C.J., 2021. The postnatal GABA shift: a developmental perspective. Neurosci. Biobehav. Rev. 124, 179–192.

Prerau, M.J., Brown, R.E., Bianchi, M.T., Ellenbogen, J.M., Purdon, P.L., 2017. Sleep neurophysiological dynamics through the lens of multitaper spectral analysis. Physiology 32 (1), 60–92.

Purdon, P.L., Pierce, E.T., Mukamel, E.A., Prerau, M.J., Walsh, J.L., Wong, K.F.K., … Brown, E.N., 2013. Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proc. Natl. Acad. Sci. 110 (12), E1142–E1151.

Sanders, R.D., Tononi, G., Laureys, S., Sleigh, J.W., Warner, D.S., 2012. Unresponsiveness ≠ Unconsciousness. Anesthesiology 116 (4), 946–959.

Schartner, M., Seth, A., Noirhomme, Q., Boly, M., Bruno, M.A., Laureys, S., Barrett, A., 2015. Complexity of multi-dimensional spontaneous EEG decreases during propofol induced general anaesthesia. PLoS ONE 10 (8), e0133532.

Shew, W.L., Yang, H., Yu, S., Roy, R., Plenz, D., 2011. Information capacity and transmission are maximized in balanced cortical networks with neuronal avalanches. J. Neurosci. 31 (1), 55–63.

Sripad, P., Rosenberg, J., Boers, F., Filss, C.P., Galldiks, N., Langen, K.J., … Dammers, J., 2020. Effect of zolpidem in the aftermath of traumatic brain injury: an MEG study. Case Rep. Neurol. Med. 2020, e8597062.

Swisher, C.B., Sinha, S.R., 2016. Utilization of quantitative EEG trends for critical care continuous EEG monitoring: a survey of neurophysiologists. J. Clin. Neurophysiol. 33 (6), 538–544.

Timmermann, C., Roseman, L., Schartner, M., Milliere, R., Williams, L.T.J., Erritzoe, D., … Carhart-Harris, R.L., 2019. Neural correlates of the DMT experience assessed with multivariate EEG. Sci. Rep. 9 (1), 16324.

Toker, D., Pappas, I., Lendner, J.D., Frohlich, J., Mateos, D.M., Muthukumaraswamy, S., … D'Esposito, M., 2022. Consciousness is supported by near-critical slow cortical electrodynamics. Proc. Natl. Acad. Sci. 119 (7), 119.

Vallat, 2018. Pingouin: statistics in Python. Journal of Open Source Software 3 (31), 1026. https://doi.org/10.21105/joss.01026.

Voytek, B., Kramer, M.A., Case, J., Lepage, K.Q., Tempesta, Z.R., Knight, R.T., Gazzaley, A., 2015. Age-related changes in 1/f neural electrophysiological noise. J. Neurosci. 35 (38), 13257–13265.

Wang, J., Noh, G.J., Choi, B.M., Ku, S.W., Joo, P., Jung, W.S., … Lee, H., 2017. Suppressed

neural complexity during ketamine- and propofol-induced unconsciousness. Neurosci. Lett. 653, 320–325.
Yoon, S., Sorbaro Sindaci, M., Goltsev, A.V., Mendes, J.F.F., 2015. Critical behavior of the relaxation rate, the susceptibility, and a pair correlation function in the Kuramoto model on scale-free networks. Phys. Rev. E 91 (3), 032814 Statistical, Nonlinear, and Soft Matter Physics...
Zhang, X.S., Roy, R.J., Jensen, E.W., 2001. EEG complexity as a measure of depth of anesthesia for patients. IEEE Trans. Biomed. Eng. 48 (12), 1424–1433.
Zhou, S., Yu, Y., 2018. Synaptic E-I Balance Underlies Efficient Neural Coding. Front. Neurosci. 12. Retrieved from https://www.frontiersin.org/article/10.3389/fnins.2018.00046 .
Zimmern, V., 2020. Why brain criticality is clinically relevant: a scoping review. Front. Neural Circuits 14. Retrieved from https://www.frontiersin.org/article/10.3389/fncir.2020.00054 .