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

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Abstract

In the human electroencephalogram (EEG), oscillatory power peaks 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 (Lendner et al. 2020). This study investigates the aperiodic EEG component of individuals in a disorder of consciousness (DOC), and how it changes in response to exposure to anesthesia. High-density EEG was recorded from 43 individuals in a DOC. To measure the brain's reaction to global perturbation, a subset of n = 16 were also exposed to a targeted infusion of propofol anesthesia. The aperiodic component was defined by the spectral slope and offset in the 1-45 Hz and 30-45 Hz range of the power spectral density. Brain network criticality and complexity were estimated using the pair correlation function (PCF) and Lempel-Ziv complexity, respectively. The level of responsiveness of all individuals in DOC was assessed using the Coma Recovery Scale-Revised (CRS-R). Recovery of consciousness was assessed three months post-EEG. At baseline, the EEG aperiodic component was more strongly correlated to the participants' level of consciousness than the oscillatory component. Anesthesia caused a steepening of the spectral slope across participants. Importantly, the change in spectral slope positively correlated with the individual participant's level of responsiveness. The spectral slope during exposure to anesthesia contained prognostic value for individuals with DOC. The anesthetic-induced change in aperiodic EEG was accompanied by loss of information-richness and a reduction in network criticality. The aperiodic EEG component in individuals with DOC has been historically neglected; this research highlights the importance of considering this measure for future research investigating brain mechanisms underlying consciousness.

Significance Statement

The analysis of human EEG has traditionally focused on oscillatory power, which is characterized by peaks above a broadband, aperiodic component in the EEG power spectral density. This study is the first to demonstrate the value of the aperiodic EEG component and specifically, its reaction to propofol anesthesia for assessing individual's level of, and capacity for, consciousness. Our results demonstrates that the pharmacological induced change in the aperiodic component accompanies the brain's loss of network criticality and complexity. Most importantly, the magnitude of brain response to propofol anesthesia relies on an individual's pre-anesthetic level of consciousness. Whereas the aperiodic EEG component has been historically neglected; this research highlights the necessity of considering this measure for future research that seeks to understand the neurophysiological underpinnings of consciousness.

Introduction

Are there signatures in human brain activity that can be used to delineate an individual's level of consciousness? During conscious wakefulness, the brain has been widely suggested to operate close to criticality — a point where the underlying network is poised between order and disorder (1–4, see 5 as a review). This balance is putatively maintained by a proper tuning between excitation and inhibition (E/I) (6, 7). Divergence from this balance has been proposed as a mechanism underlying pharmacologically induced and pathological loss of consciousness (4, 8, 9). This is a promising theoretical framework for the assessment of consciousness, especially in individuals who are behaviorally unresponsive (4, 10, 11).

Individuals in disorders of consciousness (DOC) following brain injury exhibit a wide range of reduced levels of awareness and arousal. As consciousness and responsiveness can be completely dissociated (12–14), the identification of behavior-independent measures of consciousness is crucial for improving clinical practice and for uncovering the mechanisms of human consciousness. Electroencephalography (EEG) is a particularly promising tool for assessing

the level of consciousness of individuals in a DOC, as it is highly accessible in the clinical setting, has few patient contraindications and can be recorded at the bedside (15).

To quantify levels of consciousness, the analysis of human EEG has traditionally focused on oscillatory patterns within specific frequency bands, which are defined by peaks in the power-spectral density (PSD) of the human EEG. 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 (16, 17). Recent advances in electrophysiology (16, 17) suggest that analyzing EEG data solely from the perspective of oscillatory patterns may lead to incomplete representations of the underlying neurophysiological processes.

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 DOC 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 (17), given that the periodic and aperiodic component may vary independently. 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 in DOC might also lead to more complete representations of the neurophysiological underpinnings of consciousness.

Additionally, recent studies have shown that the properties of the aperiodic EEG contain information about consciousness, which are neglected in traditional oscillation-based analyses (10, 11). The aperiodic EEG and has been linked to the local E/I balance (18–20) and divergence from criticality (4). Being correlated to established consciousness metrics, such as the Perturbation Complexity Index (10, 21) and signal complexity (20), the aperiodic component has shown much promise for the investigation of mechanisms underlying consciousness. States of unconsciousness, such as non-rapid eye movement sleep (11) and anesthetic-induced unconsciousness (10, 11) 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 (18, 22). As such, the aperiodic component has been widely proposed for the assessment of individuals in a DOC (7, 8).

Using EEG recorded under various conditions of pharmacologically and pathologically induced unconsciousness, this study aimed to characterize the aperiodic component associated with consciousness for individuals in DOC, and in particular, how this component changes in response to exposure to anesthesia. General anesthesia is known to reliably reduce levels of consciousness *and* responsiveness by globally perturbing brain networks underlying consciousness (23). Investigating the anesthetic-induced change of the aperiodic component in individuals in DOC provides a unique perspective on mechanisms underlying human consciousness. We first hypothesized that the aperiodic EEG component would have diagnostic value for individuals in DOC 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.

Results

This study combined two existing datasets of DOC participants (n= 43), a subset of whom (n= 16) were exposed to a targeted infusion of propofol anesthesia (see Methods). To characterize the aperiodic EEG component associated with level of consciousness, we first analyzed an existing dataset of 128-channel EEG recorded from 43 individuals in DOC at resting state. As a surrogate for consciousness, the level of responsiveness of each participant was assessed by a trained experimenter using the Coma Recovery Scale-Revised (CRS-R) (24). For participants in an acute DOC (n = 18), recovery of consciousness was assessed three months post-EEG. At this time, six

participants had recovered full consciousness (i.e., were able to respond verbally and consistently follow commands) (see Methods). The PSD was calculated using the Multitaper method. The aperiodic component of the EEG was defined by the offset and slope of the PSD (i.e., a steeper slope indicating faster decay of power over frequencies). Both parameters of the aperiodic component were estimated from 1-45 Hz using the 'Fitting oscillations and one over f' (FOOOF) algorithm (16) (see Methods). Oscillatory power in the delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-45 Hz) bandwidth was calculated before and after the removal of the aperiodic component. The detection of oscillatory peak frequency was performed using the FOOOF algorithm.

Aperiodic EEG component contains more diagnostic value than oscillatory power for individuals in a DOC

Splitting the PSD into aperiodic and oscillatory components (see Fig. 1A) revealed a positive correlation between the slope of the aperiodic component and participants' CRS-R score (r= 0.38, p=0.01, 95% CI [0.14, 0.57]), with flatter slope indicating higher levels of responsiveness (see Fig. 1D). In contrast to previous research (25, 26), we did not find a significant correlation between spectral power in any frequency band and participants' CRS-R score (see Fig.1B, Fig.S1 for all frequency bands). The oscillatory-only component (i.e., after removal of the aperiodic component) was also not significantly correlated to CRS-R score (see Fig. 1C, Fig. S1 for all frequency bands).

We conducted a multiple regression analysis to investigate the diagnostic information of the aperiodic component over and above the traditional power analysis. Combining oscillatory power over five canonical frequency bands (i.e., delta, theta, alpha, beta, gamma without removing the aperiodic component) and aperiodic features (i.e., spectral slope and offset) in one model (see Fig. 1E), the spectral slope (β = 1.56, p=0.002) was the only significant predictor of participants' CRS-R score (see Table 1). A forward feature selection revealed that the spectral slope alone explained 12.9% of the variance (R^2=0.129, F(1,40)=6.78, p=0.013).

An oscillatory peak could be identified in only 12 out of 43 individuals in DOC (see Fig. S2). 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 = 12) correlated with individuals' CRS-R score (see Fig. S2, see Discussion). Most importantly, no oscillatory peak was detected in the remaining 31 participants, leaving solely the aperiodic EEG component for analysis.

To control for known changes of the aperiodic component over lifespan (27), all models were controlled for participants' age, which correlated positively with participants CRS-R score (R^2=0.11, F(1,41)=5.10, p=0.03) (see Table 1). 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 DOC, compared to individuals with chronic DOC (t(41) = 2.63, p=0.01) (see Fig. S1). There was no significant difference in the spectral slope or the identified peak between participants who did or did not recover consciousness. In this analysis, the aperiodic component was estimated using the 'knee mode' of the FOOOF algorithm (min_peak_height=0.1, max_n_peaks=10) (16); all results were replicated using the 'fixed mode' (see Fig. S1).

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

Measuring the brain's reaction to perturbations has shown strong potential for the assessment of individuals in altered states of consciousness (21, 28) (see Discussion). General anesthesia is known to globally perturb brain networks, resulting in loss of consciousness *and* responsiveness. We investigated how the global perturbation of the brain network using propofol anesthesia alters the spectral slope in individuals in DOC and whether this response contains information about an individual's pre-anesthetic level of consciousness. Given that the spectral slope in healthy adult

EEG steepens in response to propofol anesthesia (10, 11), we hypothesized that larger steepening of the spectral slope in response to anesthesia would be associated with higher levels of consciousness.

We analyzed an existing dataset of 16 individuals in DOC undergoing a protocol of propofol anesthesia (see Methods). We compared 5 minutes of 128-channel EEG recorded prior to the anesthetic protocol (i.e., Baseline state) and during propofol anesthesia (i.e., Anesthesia state). For individuals in an acute DOC (n = 11), recovery of consciousness was assessed three months post-EEG. At this time, five participants had recovered full consciousness (i.e., were able to respond verbally and consistently follow commands), four participants did not recover consciousness and two participants had life-sustaining treatment withdrawn (see Methods). The aperiodic component of the EEG was defined by the offset and slope of the PSD and estimated using the FOOOF algorithm (see Methods). The propofol-induced change of the aperiodic component Δslope and Δoffset was defined by the difference between the value in the Baseline and Anesthesia conditions (Baseline − Anesthesia). In order 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 (10, 11), we also assessed the spectral slope in the 30-45 Hz range.

Anesthesia significantly steepened the spectral slope in the 30-45 Hz range ($t(15) = 4.554$, $p < 0.001$) and the 1-45 Hz range ($t(15) = 2.542$, $p < 0.05$) (see Fig. 2A, 2B). Anesthesia had a significant effect on the spectral offset in the 30-45 Hz ($t(15) = -3.685$, $p < 0.01$), but not in the 1-45 Hz range (see Fig. S3). Most interestingly, the anesthetic-induced change of both aperiodic parameters Δslope ($R^2=0.23$, $F(1,13)=6.33$, $p<0.05$) and Δoffset ($R^2=0.22$, $F(1,13)=5.85$, $p<0.05$) in the 30-45 Hz range correlated positively with participant's CRS-R score (see Fig. S3). Participants with a higher CRS-R score exhibited a larger steepening of the slope in response to propofol anesthesia. The Δslope in both frequency ranges were dependent on the spectral slope at Baseline ($r = 0.53$, $p<0.05$), with a flatter spectral slope indicating a stronger change in response to propofol (see Fig. S3).

Contradicting previous research in healthy adults (10, 11), some participants exhibited a flattening of the spectral slope in response to exposure to anesthesia (see Fig. 2B, see Discussion). The absolute value of Δslope strengthened the correlation to participants CRS-R score ($R^2=0.30$, $F(1,13)=9.62$, $p<0.01$), with a higher CRS-R score indicating a stronger change of the aperiodic component in response to propofol (see Fig. 2D). This effect could not be replicated in the 1-45 Hz range. 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 Fig. 2C). Participants' Δslope did not differ between chronic and acute states (see Fig. S3).

The aperiodic EEG component during exposure to anesthesia contains prognostic information for individuals in a DOC

During the anesthetized state, the 1-45 Hz aperiodic EEG component distinguished participants who recovered consciousness from those who did not recover consciousness (see Fig. 2E). Participants who recovered consciousness exhibited a significantly steeper spectral slope ($t(7) = -3.57$, $p < 0.01$) and higher offset ($t(7) = 2.50$, $p < 0.05$), compared to participants who did not recover consciousness. There was no prognostic value in the spectral slope at Baseline, nor in the propofol-induced change of the aperiodic component. The effect was not replicated in the 30-45 Hz range.

Propofol-induced loss of criticality is accompanied by change in the EEG spectral slope

During conscious wakefulness, the brain is considered to be tuned to a critical state, which maximizes the network's information-richness, computational efficiency and sensitivity to perturbations (1, 2). The brain's reaction to general anesthesia is characterized by a divergence

from this critical state (4, see 5 as a review, 8, 9, 29), resulting in a loss of network integration (30–32), signal complexity and sensitivity to perturbations (33, 34). The aperiodic component of the EEG is strongly linked to these measures and has been correlated with signal complexity (20, 35), the perturbation complexity index (10) and the brain's balance between excitation and inhibition (20). Further, Toker et al. (4) demonstrated that the propofol-induced steepening of the spectral slope accompanies the brain's distancing from criticality. To further investigate the mechanism underlying the change in the aperiodic component, we investigated how the propofol-induced change of the spectral slope was related to alterations in network criticality and complexity. We hypothesized that there would be a strong alignment between the propofol-induced change in the EEG aperiodic component and changes in network complexity and criticality.

Signal complexity was estimated using the Lempel-Ziv complexity (LZC) (36) on the median-binarized time series (see Methods). The network criticality was estimated using the pair correlation function (PCF), which has previously been linked to the information integration of the underlying brain network (29). Both measures were estimated in the 1-45 Hz range (see Methods, see Discussion). The propofol-induced change of the signal complexity and network criticality was defined by the difference between the values in the Baseline and Anesthesia condition (Baseline – Anesthesia).

We first assessed how the magnitude of change of the spectral slope depended on the brain's signal complexity and criticality at the Baseline state. In the 1-45 Hz range, the absolute change of the spectral slope correlated with the Baseline signal complexity (R^2=0.57, F(1,14)=18.25, p<0.001) and criticality (R^2=0.25, F(1,14)=4.72, p<0.05) (see Fig. 3A). Participants with higher complexity and criticality exhibited a stronger steepening of the spectral slope following exposure to propofol anesthesia. In the 30-45 Hz range, the change of slope was strongly related to the baseline network criticality (R^2=0.44, F(1,14)=11.13, p<0.01), but did not depend on signal complexity.

Additionally, we demonstrated how the change of spectral slope not only depended on the properties of the brain at Baseline, but also reflected the brain's anesthetic-induced loss of criticality. The propofol-induced change in network criticality positively correlated with the change of the spectral slope in the 1-45 Hz (R^2=0.44, F(1,14)=11.09, p<0.01), and 30-45 Hz range (R^2=0.36, F(1,14)=7.93, p<0.05) (see Fig. 3B). Similarly, the change in network complexity was positively correlated to the change of the spectral slope in the 1-45 (R^2=0.80, F(1,14)=55.63, p<0.001), and 30-45 Hz range (R^2=0.32, F(1,14)=6.50, p<0.05). Most interestingly, participants who showed a propofol-induced flattening of the spectral slope (see Fig. 2B, 3B) also exhibited an increased signal complexity and network criticality in the anesthetized state (see Discussion).

Cumulatively, the magnitude of propofol-induced change of the spectral slope was highly dependent on the brain's signal complexity and criticality at Baseline, with a more complex and critical brain indicating stronger alteration of the spectral slope in response to propofol anesthesia. Additionally, the change of the spectral slope accompanied the propofol-induced loss of network complexity and criticality. In line with previous research (20, 35), the spectral slope (R^2=0.55, F(1,41)=50.43, p<0.001) and offset (R^2=0.51, F(1,41)=43.51, p<0.001) at baseline in the 1-45 Hz, but not the 30-45 Hz range significantly correlated with signal complexity (see Fig. S4).

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. The significance of this finding is underscored by the fact that although 75% of the DOC participants 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 (28), we also investigated the prognostic value of the aperiodic EEG component change upon exposure to propofol. We showed that the propofol-induced change of the EEG aperiodic component accompanied loss of network criticality and was correlated with the individuals' level of consciousness. Cumulatively, our results highlight the urgent need to reconsider analysis of DOC brain activity in light of the diagnostic and prognostic information contained in the traditionally discarded aperiodic EEG component. Our results further support the proposition that the brain of individuals in DOC operates far from a critical point (4), resulting in weaker network susceptibility to global perturbations, such as propofol anesthesia.

It has been widely proposed that the diagnostic and prognostic power of the EEG aperiodic component should be investigated in brain-injured, unresponsive patients (10, 11). The strong evidence that the aperiodic EEG component distinguishes states of wakefulness from sleep (11) and general anesthesia (10, 11) motivated investigations of diagnostic value of this signal for unresponsive patients. In a clinical population, Lanzone et al. (37) proposed the aperiodic slope as an index for longitudinal recovery from stroke. To date, only a single study by Alnes et al. (35) 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 DOC are overshadowed by the known effect of anesthesia on the spectral slope. Our study compares the aperiodic EEG component for DOC participants before and during exposure to 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 has been described through alterations in the power of canonical EEG frequency bands (see 38 as a review). Recent best practice in EEG analysis recommends removing the aperiodic component from the signal prior to power analysis (17). However, the EEG of individuals in 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 participant's CRS-R score and power in alpha (25) and delta bandwidth (26), we did not reproduce these results in the current study. We consider two possible explanations for this discrepancy: first, whereas Chennu et al. (25) included individuals with CRS-R score above 7, only 24% of the participants in this 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 (17). Thus, the previously shown increased delta power in individuals with lower levels of consciousness (25, 26) might in fact be epiphenomenal to a steepening of the steeper spectral slope, instead of oscillatory power.

Other studies have also presented evidence for the role of EEG oscillatory power in the assessment of DOC. Lechinger et al (26) 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 (26). 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 6 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 diagnostic value for individuals in DOC might be fully attributable to the aperiodic component.

Despite strong evidence that the spectral slope is related to consciousness (10, 11), there is disagreement about whether it is a measure of arousal (i.e. vigilance) (11) or the level of consciousness (i.e. awareness) (10). Rather than framing our results within these dimensions – which have been criticized as failing to represent the multifaceted nature of consciousness and its disorders (39) -- 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 (19, 20). Consciousness has been proposed to be underpinned by an optimal E/I balance (4), which tunes the brain towards a state of criticality and information-richness (7). When this balance is disrupted (i.e. more inhibition than excitation) the network diverges from criticality, exhibits a steeper spectral slope (see 5 as a review, 19, 20) and reduced signal complexity (20).

Exposure to the inhibitory drug propofol causes steepening of the spectral slope (10, 11), 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 might have less capacity to shift, as it is closer to maximum imbalance. In other words, the already-steepened spectral slope in comatose patients could reflect the brain's high imbalance and distance to 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 (28). Thus, one potential interpretation of our results is that individuals in DOC 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 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. (4) observed a similar inconsistency, with one individual in DOC exhibiting a reduction in chaoticity after regaining consciousness. Although an increase of complexity and flattening of the spectral slope following exposure to anesthesia is counterintuitive for healthy individuals, DOC is a heterogenous set of conditions. The spectral slope in the 1-45 Hz range at baseline clearly separated individuals with DOC 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. 2B). Further characterization of the clinical differences between these groups is warranted in 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 (CRS-R) (24), which is a behavioral scale for the assessment of responsiveness. The resulting score is widely used as a surrogate measure of consciousness. However in DOC, consciousness can be fully dissociated from behavior (12–14). 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, DOC participants 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.

Second, participants in this study were recruited after a variety of brain injuries, including stroke, traumatic and anoxic brain injury. Although the spectral slope is more negative in the hemisphere most affected by a stroke, (37), this study did not account for the location of the brain injury. 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. Third, this study explored the link between the aperiodic component and criticality, measured by the PCF (29). Whereas this measure of criticality is commonly estimated on oscillation in the alpha frequency band (29, 40), the lack of oscillatory patterns in this studies population did not justify the use of a narrow frequency band. The PCF is only one measure within a large methodological framework of network criticality (see 5 as a review); the broader exploration of the aperiodic component and its relation to measures of criticality, which do not rely on oscillation, is strongly recommended for future research. Fourth, the detection of oscillatory peaks in the first part of the analysis was performed on the electrode-averaged spectrum. Whereas most individual's electrode-averaged PSD did not exhibit oscillatory peaks, we cannot exclude the possibility of small oscillatory peaks on the level of single electrodes.

In conclusion, we have demonstrated the value of the aperiodic EEG component for the assessment of individuals in a DOC 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 accompanies the brain's loss of criticality and complexity and is informative about an individual's baseline level of consciousness and their potential to recover consciousness. 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 DOC.

Materials and Methods

Participants and anesthetic protocol

This study combined two existing datasets of DOC participants (i.e., one dataset of Baseline EEG recordings and one dataset of individuals in DOC, undergoing an anesthetic protocol). In total, 43 individuals in a DOC (22 male, 42 ±15.13 years old) were included in this study. Individuals in a DOC were included following acquired brain injury (anoxic, traumatic, hypoxic brain injury, stroke) and assessed by a trained experimenter using the Coma Recovery Scale-Revised (CRS-R) (24). 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 DOC participants, 14 were in MCS, 25 in UWS and four in a coma (CRS-R = 5.88 ± 4.02). For participants in an acute DOC (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). Nine participants did not recover consciousness remained in a DOC. Three participants had life-sustaining treatment withdrawn and were not excluded from the analysis of prognostic value.

Sixteen (n=16) of the above described individuals in a DOC (5 male, 44 ±18.24 years old) underwent an anesthetic protocol, explained in (41). 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 minutes resting state prior to the start of the anesthetic protocol (referred to as: Baseline state) as well as the period of 5 minutes 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 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), four participants did not recover consciousness and two participants had life-sustaining treatment withdrawn.

Electroencephalography data

Data in both datasets were 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 participants were recorded using a 64-channel EEG system. Prior to analysis, the raw signal was filtered between 0.5 to 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 epoched in non-overlapping segments of 10 seconds. 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 (42).

Spectral slope and power analysis

The power spectra were calculated for every electrode and epoch, using the Multitaper approach (43). 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 (43). The aperiodic component was defined by the EEG spectral slope and offset which were calculated using the FOOOF package (16). 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 (10, 11), the spectral slope was herein defined by $-\chi$. 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 Fig. S1) and was presented in this paper. The model error and analysis using the knee mode is provided in the supplementary material (see Fig. S1). The power spectra, as well as the spectral slope were calculated for every participant, epoch, and electrode independently and averaged subsequently. Is it to note 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. removal of the aperiodic component) using the FOOOF package (16). 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 spectral slope was defined as the distance between the baseline value and the value in the anesthetized state (i.e. Baseline − Anesthesia).

Complexity and Criticality

After binarizing every channel using their individual medians, complexity was calculated using the Lempel-Ziv Complexity (36) implementation of the AntroPy toolbox (44). Complexity was calculated for every channel and epoch individually and averaged subsequently. Criticality of the brain network was defined using the pair correlation function, which is an estimate of global phase synchronization or network susceptibility (29, 40). Both values were estimated on the full frequency range (1-45Hz). The PCF was defined as the average PCF per channel. The propofol-induced change in both measures was defined as the distance between the baseline value to the value in the anesthetized state.

Statistical analysis

Statistical analysis was performed using JASP (45). The link between the oscillatory and aperiodic component with participants' CRS-R score was assessed using Pearson correlation and multivariate linear regression, preconditioned on participants age. Confidence intervals were estimated using bootstrapping (1000 iterations). The change of the spectral slope in response to propofol anesthesia was assessed using repeated measures t-test. Group differences between recovered and non-recovered participants were assessed using independent t-test.

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Figures and Tables

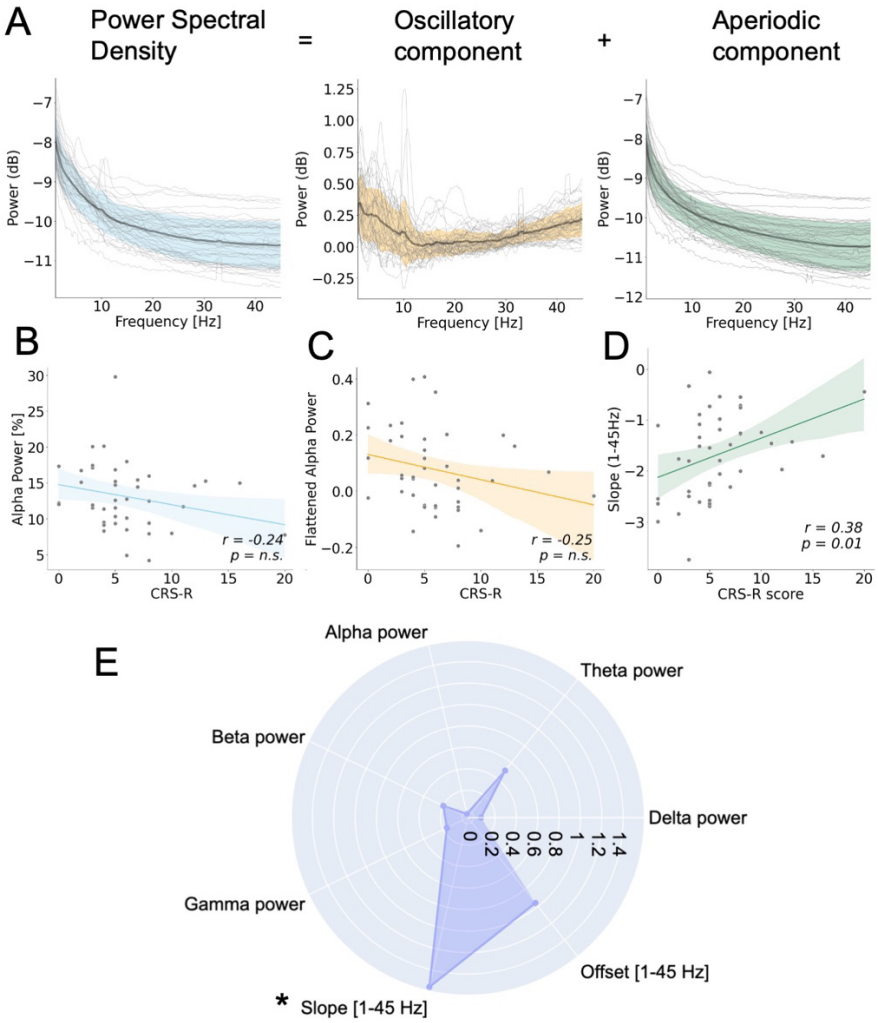

Figure 1. *Diagnostic value of EEG spectral properties in DOC.* ***(A)*** *The power spectral density of individuals in DOC (blue) separates into an oscillatory component (orange) and an aperiodic component (green). Light grey lines represent individual subjects; darker lines represent the group average and standard deviation.* ***(B)*** *The traditional power analysis of oscillatory EEG in the alpha bandwidth does not correlate to individual's level of responsiveness, 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 correlate to individuals' level of responsiveness, as measured by the CRS-R score.* ***(D)*** *The aperiodic component of individuals EEG significantly correlates to individuals level of responsiveness.* ***(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 responsiveness.*

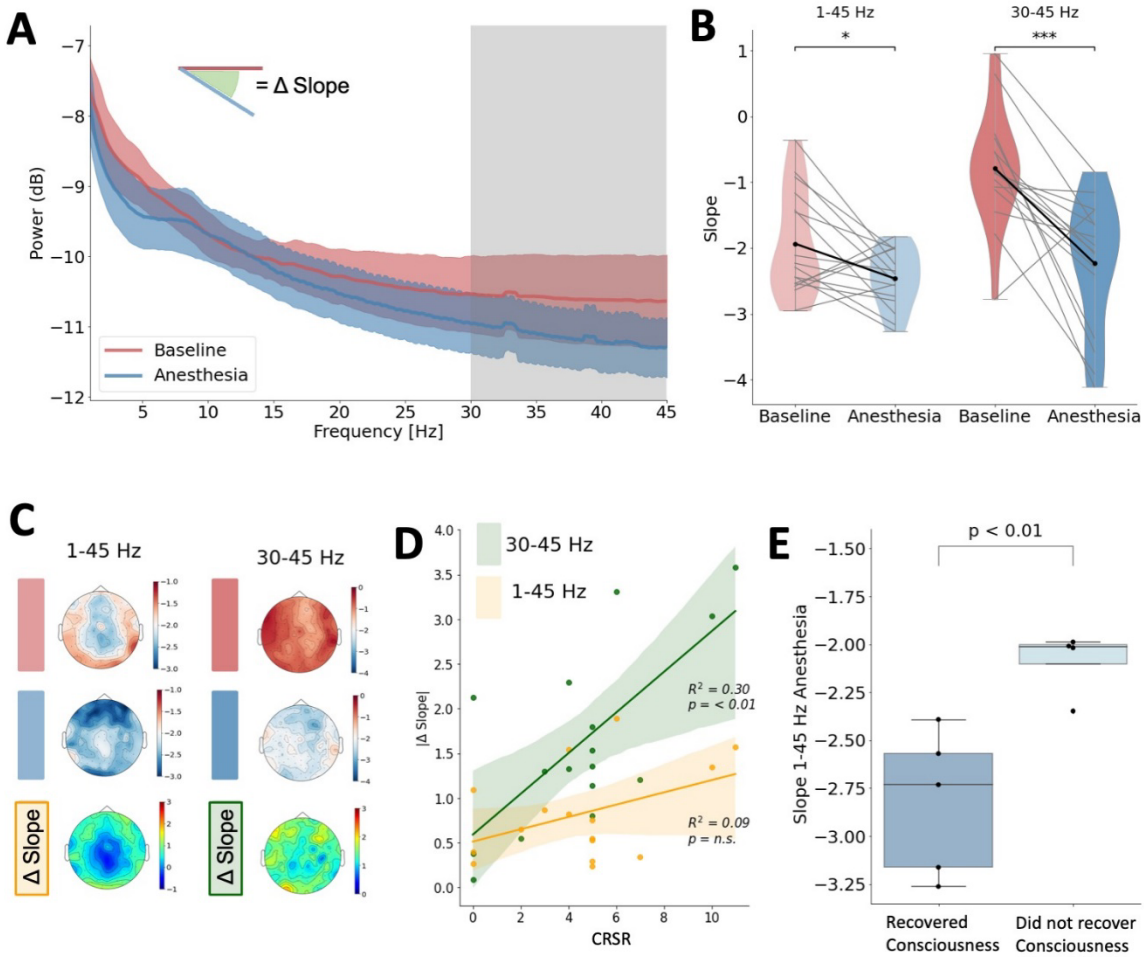

Figure 2. *Alterations of the spectral slope in DOC and general anesthesia.* ***(A)*** *Power spectral density of Baseline (red) and Anesthesia state (blue), averaged across participants.* ***(B)*** *Change in spectral slope in response to propofol anesthesia in 1-45 Hz (left) and 30-45 Hz (right).* ***(C)*** *Group-averaged spatial distribution of the spectral slope at Baseline and Anesthesia state and the change in spectral slope (Δ Slope).* ***(D)*** *The absolute change in spectral slope over all channels in the 30-45 Hz range correlates with participants' CRS-R score.* ***(E)*** *The spectral slope during anesthesia in the 1-45 Hz range differs between individuals who did and did not recover consciousness after DOC. Error bars represent standard errors.*

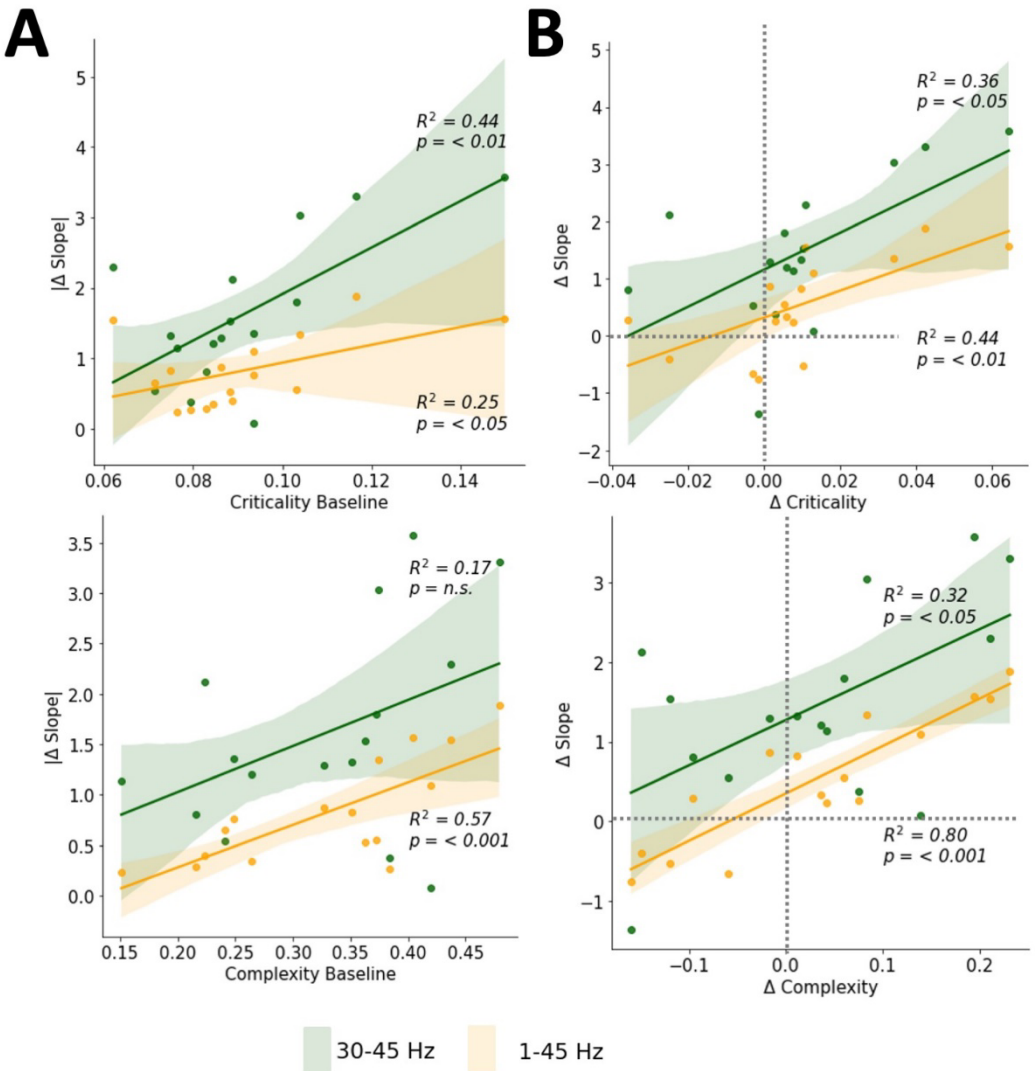

Figure 3. Relation between the spectral slope, signal complexity and network criticality in individuals with DOC **A)** The absolute anesthetic-induced change of spectral slope correlates with the pre-anesthetic criticality (top) and complexity (bottom). **B)** Propofol-induced change of spectral slope accompanies the brains propofol-induced changes in criticality (top) and complexity (bottom).

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

Coefficients

						95% CI	
	b	**SE**	**β**	**t**	**p**	**Lower**	**Upper**
(Intercept)	30.165	54.261		0.556	0.582	-79.992	140.321
Age	-0.05	0.038	-0.189	-1.338	0.19	-0.127	0.026
Slope [1-45 Hz]	7.595	2.294	1.561	3.311	**0.002**	2.938	12.252
Offset [1-45 Hz]	2.869	1.632	0.96	1.758	0.087	-0.444	6.181
Power Delta	0.096	0.857	0.068	0.112	0.912	-1.645	1.836
Power Theta	0.526	0.457	0.506	1.152	0.257	-0.402	1.454
Power Alpha	-0.019	0.442	-0.022	-0.043	0.966	-0.916	0.878
Power Beta	0.274	0.34	0.198	0.805	0.426	-0.417	0.965
Power Gamma	0.261	0.282	0.162	0.927	0.360	-0.311	0.834

Note: Null model contained Age, SE: Standard Error