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“Spectral Peak Analysis and Intrinsic Neural Timescales as Markers for the State of Consciousness”

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Oh, I got plenty of time
Oh, you got light in your eyes
And you're standing here beside me
I love the passing of time
Never for money, always for love
Cover up and say goodnight, say goodnight

Ai miei genitori.

Spectral Peak Analysis and Intrinsic Neural Timescales as Markers for the State of Consciousness

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Abstract

Resting state EEG in patients with disorders of consciousness (DOC) is characterized by an increase of power in the delta frequency band and a concurrent decrease in the alpha range, equivalent to a weakening or disappearance of the alpha peak. Prolongation of Intrinsic Neural Timescales (INTs) is also associated with DOCs. Together, this raises the question whether the decreased alpha peak relates to the prolonged INTs and, importantly, how that can be used for diagnosing the state of consciousness in DOC individuals. Analyzing resting state EEG recordings from both healthy subjects and DOC patients, we measure INTs through autocorrelation window (ACW) and develop novel measures to quantify the weakening of the alpha peak. First, we replicate previous findings of prolonged ACW in DOC patients. We then identify significantly lower alpha peak measures in DOC compared to controls. Interestingly, spectral peaks shift from the alpha to the theta range in several DOC subjects while such change is absent in healthy controls. Next, our study reveals a close relationship between ACW and alpha peak in both healthy and DOC subjects, a correlation that holds for theta peaks in DOC. Further, the prolonged ACW correlates with the state of consciousness, as quantified by the Coma Recovery Scale-Revised (CRS-R), and mediates the relationship between theta peak and CRS-R. Finally, through split analyses and machine learning, we show that ACW and alpha peak measures conjointly distinguish healthy controls and DOC patients with high accuracy (95.5%). In conclusion, we demonstrate that the prolongation of ACW, together with spectral peak measures, holds promise to serve as additional EEG biomarkers for diagnosing the state of consciousness in DOC subjects.

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Introduction

The diagnosis of disorders of consciousness (DOC) remains an ongoing challenge for both clinicians and researchers alike, particularly regarding differential diagnosis between minimally conscious state (MCS) and unresponsive wakefulness state (UWS), also known as vegetative state (VS). In recent decades, neurobehavioral assessment tools such as the Coma Recovery Scale–Revised (CRS-R)[1,2] have represented a significant improvement over diagnosis by clinical consensus[3] allowing for quantitative and standardized diagnosis. Extending such behavioral assessment, recent research has focused on identifying more objective and reproducible neurobiological markers through the use of neuroimaging.

Among these approaches, EEG has gained attention due to its economic feasibility and potential for bedside use. Several EEG markers, such as the perturbational complexity index (PCI) and other measures of informational complexity,[4–9] evoked potentials[10,11] and spectral analysis[12–15] have shown promising results. However, clinical usage of these markers for differential diagnosis remains an ongoing challenge.

Research on spectral analysis has revealed that the alpha frequency range (7.5 – 13 Hz) exhibits a decrease in power in DOC patients.[9,12,16,17] Recent machine learning studies have further confirmed the importance of alpha, as well as the theta and delta bands, as key electrophysiological markers in classifying DOC patients and discriminating between MCS and UWS/VS.[9,16] Typically, the alpha band exhibits a peak in power among healthy subjects.[18,19] However, the exact quantification of the alpha peak including its decrease in power in DOC individuals and its potential relation to the state of consciousness remains an open issue. Addressing this gap in our knowledge constitutes the primary goal of our paper.

Extending beyond spectral measures, recent studies have focused on Intrinsic Neural Timescales (INTs), the timescales at which single neurons and/or neural populations process incoming information.[20–22] INTs, measured through the autocorrelation window (ACW), are abnormally prolonged in states of decreased consciousness, such as sleep, anesthesia, and DOC.[23,24] This prompts the question of whether the prolongation of ACW in DOC patients could relate to the weakening or disappearance of their alpha peak, and whether the two conjointly modulate the state of consciousness.

The primary goal of our EEG study was to investigate and quantify the changes in the alpha peak as well as how they relate to INTs, measured through ACW, in both healthy controls and DOC patients. To quantify the weakening or disappearance of the alpha peak in DOC we introduced novel measures by utilizing peak analysis. Additionally, we aimed at replicating previous results of a prolonged ACW in DOC.[12,23,24] Given previous findings, we hypothesized that DOC subjects would show a prolongation of ACW alongside a significant reduction in the novel alpha peak measures. The second specific aim involved establishing a relationship between alpha peak measures, ACW and the state of consciousness, as measured by CRS-R. We anticipated negative correlations between alpha peak measures and ACW, both of which are expected to relate to the level of consciousness (CRS-R). The third specific aim probed whether our measures enable the prediction of the state of consciousness, as tested through split analyses and machine learning. Building on our previous work,[12,23,24] we hypothesized that ACW, particularly in its relation to alpha peak measures, might carry potential for accurately classifying patients based on the state of consciousness, as measured by CRS-R.

In this study, we analyzed resting state EEG recordings obtained from eighty-eight DOC patients and twenty-five recordings from twenty-five healthy controls, focusing on three frontal (i.e. Fz, F1, F2) and three occipital electrodes (i.e. Oz, O1, O2). Our initial emphasis was on the alpha peak and its disappearance in DOC subjects. To address this issue, we developed novel measures to quantify the alpha peak itself, conducting a peak analysis on the power-spectral density (PSD) derived from the EEG signals, identifying five peak-related measures – *power*, *power ratio*, *prominence*, *width* and *frequency*. To avoid restricting our analysis to the alpha range, we also incorporated two non-peak measures, *maximum power* and *minimum mower*. These measures explore the delta and gamma frequency ranges, respectively, taking into account the inverse exponential trend of the PSD. For clarity, we refer to the peak-related measures as "peak measures" while both peak-related and non-peak-related measures combined as "spectral measures". Over the same electrodes, we also measured Intrinsic Neural Timescales using the autocorrelation function (ACF). Following established methods, we represented INTs via the autocorrelation window (ACW),[23–28] which in EEG and MEG studies is defined as the first point where the autocorrelation value reaches a specified threshold.[23,24,26,27]

Our first finding highlights the scarcity of alpha peaks (7.5 – 13 Hz) in DOC patients compared to controls (7 and 13 alpha peaks, respectively for frontal and occipital in DOC patients, and 22 both for frontal and occipital in healthy controls), with DOC individuals displaying more peaks in the theta frequency range (3 – 7.5 Hz). This finding converges with results observed in MCS subjects[29] and also in the PSDs obtained in healthy subjects under ketamine.[6,30,31] We then compared spectral measures between controls and the subset of DOC patients exhibiting alpha peaks and found that healthy subjects have higher values in all measures, except *maximum power* (higher in DOC patients) and *width* (no significant differences). Shifting our focus to INTs, we found prolonged ACW in DOC subjects compared to controls, a result consistent with prior research.[23,24] We then linked INTs to the alpha peak, finding robust correlations between spectral measures and ACW, in both healthy individuals and patients with disorders of consciousness. Correlations between ACW and spectral measures persisted in DOC patients displaying theta peaks. Further, we aimed at establishing a relationship between both neural measures with the level of consciousness in DOC, as measured with the Coma Recovery Scale-Revised. We observed that ACW correlates negatively with CRS-R and identified two significant mediation models with ACW mediating the impact of peak measures on the CRS-R in DOC subjects with theta peak. Finally, we conducted split analyses and machine learning, showing the potential utility of ACW conjointly with spectral measures derived from peak analysis as additional diagnostic biomarkers in assessing the state of consciousness.

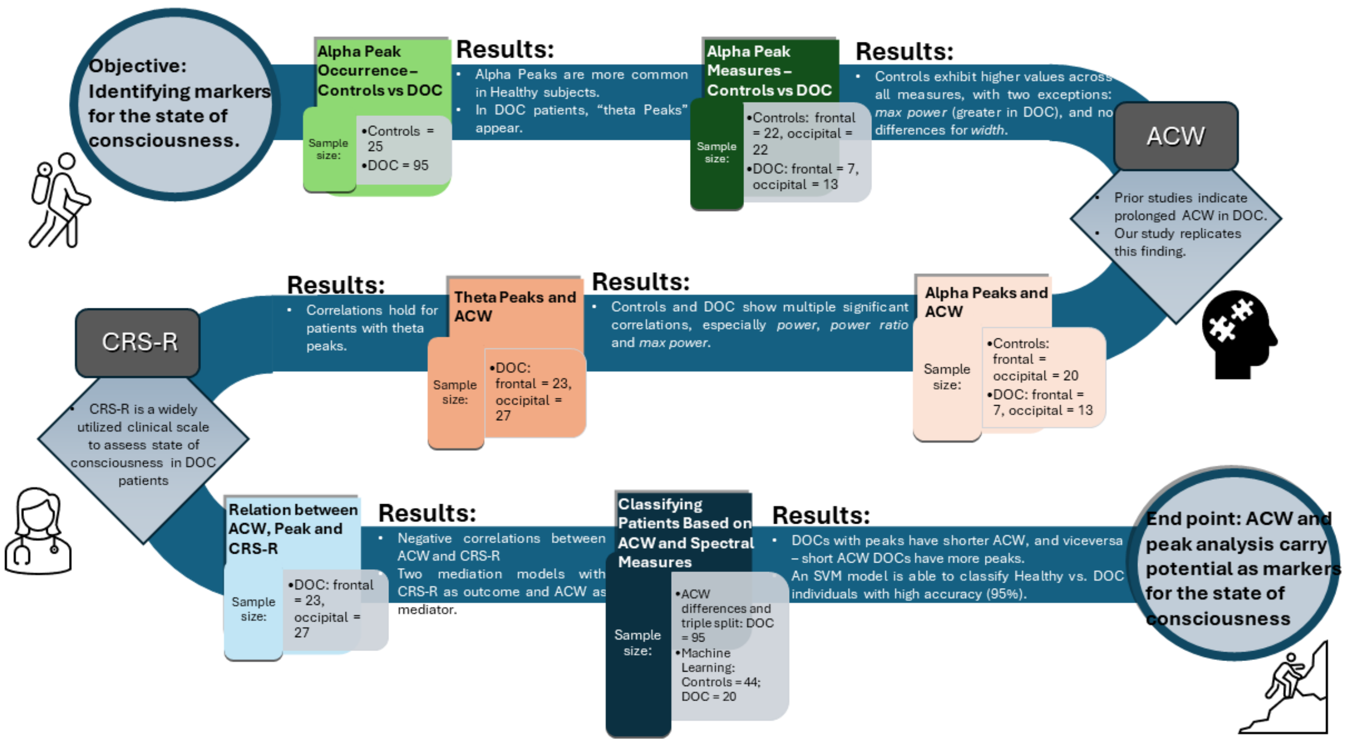

Figure 1 - Roadmap.

We commenced by examining the prevalence of alpha peaks in healthy controls compared to DOC individuals. Employing peak analysis, we demonstrate the weakening and disappearance of the alpha peak in DOC patients, along with its shift to the theta range. Building on the replicated finding of prolonged INTs in DOC subjects, we establish strong correlations between our peak measures and ACW – correlations that hold for patients displaying theta peaks. The relationship between ACW, peak measurements and the state of consciousness (as assessed by CRS-R) is intricate: we identify negative correlations between ACW and CRS-R, with mediation analysis suggesting that INTs take on a mediating role between theta peak and CRS-R. Finally, split analyses hint at the possibility of using ACW and our peak measures as markers for the state of consciousness: a Support Vector Machine (SVM) model achieves high accuracy in classifying healthy controls vs. DOC.

Methods and Materials

Participants

Ninety-five resting state EEG recordings (MCS = 47; UWS = 48) were obtained from eighty-eight patients with disorders of consciousness (mean age = 46.91 ± 15.82; sex-ratio = 2.38; etiology: stroke = 44; anoxia = 6; TBI = 38). On admission patients were assessed by trained clinicians with the Glasgow Coma Scale (GCS).[32] Further evaluation was obtained with the JFK Coma Recovery Scale–Revised (CRS-R)[1] immediately preceding the recording session. The recording session lasted for a minimum of 5 minutes and employed a 256-channel system (GES 300, Electrical Geodesics, Inc., USA). Before starting the recording, examiners performed the Arousal Facilitation Protocol[1] to induce wakefulness. No sedative agents were administered 24 hours prior to recording. Possible sources of electronic noise were reduced, and participants wore soundproof earmuffs (3 M Company) to attenuate environmental noise.

For the control sample, 25 healthy participants (age 24.56 ± 0.71 years; M/F sex-ratio = 0.94) underwent a similar procedure: a 5-minute resting-state recording session utilizing the same EEG recording system (GES 300, Electrical Geodesics, Inc., USA). Controls were asked to lay in bed and keep their eyes open: this was done to mimic the recording experience of DOC patients as much as possible. EEG data was re-referenced online to Cz and acquired at a sampling rate of 1000 Hz, while keeping impedance of all electrodes below 20 KΩ.

Ethics statement

Before participation, informed written consent was obtained from all participants (or from their caregivers). The study was approved by the Ethical Committee of the Huashan Hospital of Fudan University (approval number HIRB-2014–281) and conducted in accordance with the Declaration of Helsinki guidelines.

Pre-processing

First, data was down sampled to 250 Hz. Then, a band-pass finite impulse response (FIR) filter between 0.5 and 40 Hz (Hamming window) was applied. Noisy channels were identified and excluded from further analysis through a semiautomatic procedure.

Criteria for rejection of noisy channels were the following: flatline channels (channels showing no activity for more than 5 seconds), highly correlating channels (threshold set at 0.8), low-frequency drifts, noisy channels and short-timed bursts not related to neural activity (threshold at SD = 5 for data portions relative to baseline). Removed channels were then interpolated with a spherical method and channel activity was re-referenced to the common average reference. Finally, all recordings were clipped to a length of exactly 5 minutes. Artifacts (i.e. eye movements, muscular noise, and heart activity) were removed through independent component analysis (ICA). [33]

Electrode selection

For our research we focused on three frontal electrodes (i.e. Fz, F1, F2) and three occipital electrodes (i.e. Oz, O1, O2), selected based on the key role played by these regions in DOC, as evidenced by consistent differences between MCS and UWS/VS.[34] Specifically, alpha band power in the frontal as well as in occipital regions has proven to be higher in MCS compared to UWS/VS[17,35,36] while delta power was found to be higher in UWS/VS over the same areas.[17,35,36] Therefore, both spectral and ACW measurements were calculated separately for these six electrodes and averaged among the frontal and occipital electrodes, respectively.

Spectral analysis

The Power Spectral Density (PSD) describes the power for each frequency component of a signal. To estimate the PSD, the Welch method was used. The method splits the EEG timeseries into windows (3 seconds, for our study) with a certain degree of overlap between them (50%, for our study) and computes a Fast Fourier Transform (FFT) for each window. It then calculates the absolute value of Fourier coefficients for each frequency, and a Hamming window is applied to all segments. Finally, the PSD is estimated by averaging across all individual periodograms.

This procedure was performed for the selected electrodes (i.e. three frontal: Fz, F1, F2; three occipital: Oz, O1, O2), and PSDs were averaged across frontal and occipital electrodes for each subject, obtaining two PSDs: one frontal and one occipital. The Y-axis was set to logarithmic scale (base 10), and further analysis was performed on such values.

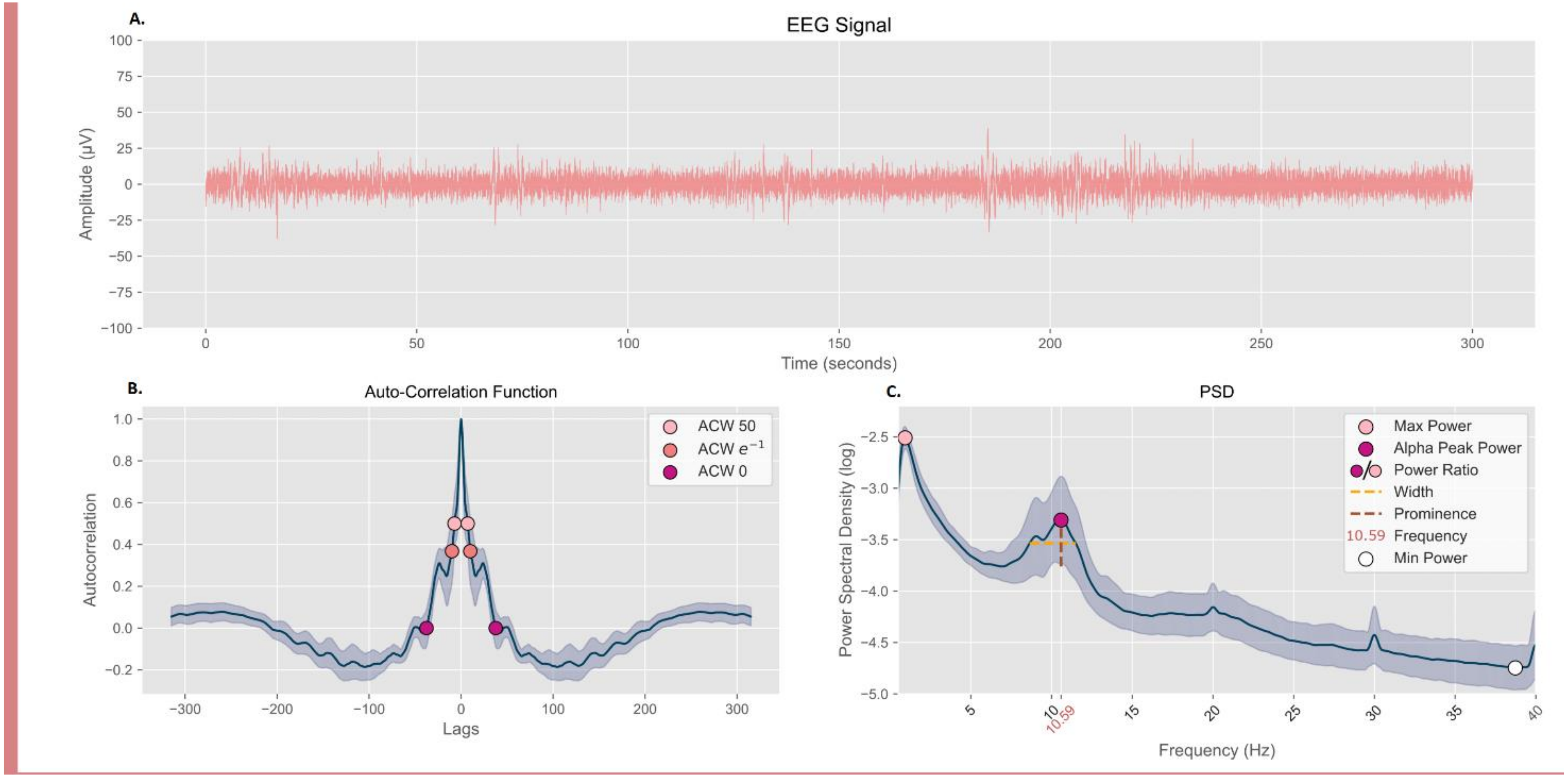

Figure 2 – From EEG to Auto-Correlation Function and Power Spectral Density.

Starting from an EEG signal (a) we measure Intrinsic Neural Timescales (INTs) using the Autocorrelation Function (b) and obtain the Power Spectral Density (PSD) via a Fast Fourier Transform (c). Panel (c) illustrates the measures we acquired through peak analysis.

Peak analysis

For peak analysis, the MATLAB function "findpeaks" (Signal Processing Toolbox) was used. The function identifies local maxima and returns its X and Y coordinates, as well as the peak's *width* and *prominence*. This function has found widespread use, with studies ranging from X-ray photoelectron spectroscopy,[37] to gait analysis in patients with Parkinson's disease[38] and has already been applied to EEG spectral analysis.[39,40]

Peak and non-peak measures are defined as follows:

'*Power*': the local maxima itself (i.e. Y-coordinate). *Power* is therefore the 'tip' of the peak (i.e. the highest point): the word 'peak' should then be intended as representing the region of the PSD encompassing a *power*, a *width*, a *prominence*, and a *frequency*.

'*Frequency*': the corresponding X-coordinate of the local maxima (i.e. the Power).

'*Prominence*': *prominence* (or 'relative height') is defined as the difference between the height of the peak and its highest minimum. To visualize this measure, the following example is used, taken from the MATLAB documentation. Picture tracing a horizontal line through the highest point of the peak, to the left and to the right of it, until the line either reaches the endpoint of the signal or crosses the signal at the slope of a higher peak. Then, calculate the minimum point in these two segments (to the left and to the right of the peak). The greater between the two values is the highest minimum and is used for the calculation of the *prominence*.

'*Width*': *width* is computed as the distance between the peak's left and right points where its descending slopes intersect with a horizontal reference line. This reference line is set, by default, to be at a height equal to the middle point of the *prominence*.

'*Maximum Power*': the maximum power value in the PSD.

'*Minimum Power*': the minimum power value in the PSD.

'*Power Ratio*': the ratio between *power* and *maximum power*.

For simplicity, we will refer to all seven measures as "spectral measures" and to the peak-related measures as "peak measures". Further details on how the findpeaks function was used are described in the Supplementary material.

A 'theta peak' was defined as a peak having its *frequency* in the 3-7.5 Hz range; an 'alpha peak' was defined as a peak having its *frequency* in the 7.5-13Hz range. When multiple peaks were found, the peak with greater *prominence* was selected and subsequently used for analysis. If the function could not identify any peaks, then the PSD was counted as ‘no peak’ (or ‘flat’). Peak and non-peak measures can be visualized in Figure 2C.

Intrinsic Neural Timescales – ACW-50, ACW-e^{-1}, ACW-0

The Auto-Correlation Function (ACF) estimates the correlation between a signal and a copy of itself, delayed in time. The Auto-Correlation Window (ACW) marks the first lag of ACF where the value of autocorrelation reaches a desired threshold. These values serve as an estimation of how quickly a signal decorrelates with itself.

For ACW-50, ACW e^{-1}, and ACW-0, time lag thresholds were set, respectively, at 0.5, e^{-1} and 0. Determining the appropriate time lag for autocorrelation of EEG timeseries is a complex task. Previous studies have utilized both ACW-50[6,23,25] and the more novel ACW-0.[24,25] For our study, we included these measures and added ACW-e^{-1}, which has been proposed in the past.[41]

Calculations were computed for the selected electrodes (i.e. three frontal: Fz, F1, F2; three occipital: Oz, O1, O2) and averaged for frontal and occipital electrodes respectively, obtaining one value for frontal electrodes, and one value for occipital electrodes, for each of the three ACW thresholds, respectively.

Statistical analysis

For differences in rates of rates of presence or absence of peak between controls and DOC patients, a Chi-Squared test was performed.

For all samples, before proceeding with further analysis, a Shapiro-Wilk test for normality was performed: for differences between spectral measures in controls and DOC patients parametric (independent t test) and non-parametric (Mann-Whitney *U* test) statistical tests were performed accordingly.

For correlations between spectral measures and ACW, no specific assumptions of linear or non-linear relationships between the variables were made. Therefore, Pearson or Spearman correlation coefficients were estimated according to the normality of sample distributions. An identical procedure was followed for figures in Supplementary material. Significance level was set to 0.05 and p values were adjusted for multiple comparisons with the Benjamini-Hochberg correction where appropriate.

For all correlations involving CRS-R, given the variable’s ordinal nature, only Spearman’s coefficient was calculated. Mediation analysis was performed with a bootstrap method (n = 5000) after standard scaling. Importantly, the exogenous variable CRS-R was treated as ordinal in the model.

For differences in the rates of presence or absence of peak after the triple-split, a Chi-Squared test was used. For the median split results an independent T-test (for *power ratio* and *power*) and a Mann-Whitney *U* test (CRS-R) were utilized.

It is essential to highlight that the frontal and occipital groups did not always consist of identical subjects. In some instances, a subject exhibited a peak in the frontal region without a corresponding peak in the occipital region, and vice versa. The reader should infer that the frontal and occipital groups comprise distinct sets of subjects, unless expressly indicated otherwise.

Machine learning

For the machine learning analysis, we employed a Support Vector Machine (SVM), due to its robustness in high-dimensional data and its effectiveness in dealing with non-linear decision boundaries.[43] The analysis used the Matlab 'fitcecoc' function, which implements Error-Correcting Output Codes (ECOC) for multiclass classification.[44,45] The function trains a classifier using SVMs with a one-against-one (OvO) coding design. The OvO approach constructs $N\times(N-1)/2$ binary SVM models, where N represents the number of classes in the dataset, ensuring effective classification across multiple classes.[44] The SVM model was trained on the training dataset along with its corresponding class labels. Throughout the training process, the model optimized the hyperparameters and determined the optimal decision boundary to maximize classification accuracy.

To evaluate the generalization performance of the SVM model and mitigate overfitting, we employed 10-fold cross-validation.

The performance of the trained SVM model was assessed using accuracy, precision, recall, F1-score, and confusion matrix analysis. Additionally, receiver operating characteristic (ROC) curves and area under the curve (AUC) values were computed to assess the model's discriminative ability across different thresholds. The average performance across all folds was then calculated to provide a robust estimate of the model's effectiveness in classifying unseen data.

Software

Pre-processing, ICA, peak analysis, spectral analysis, ACW extraction and machine learning were performed on the MATLAB software (The MathWorks, 2023b) and the EEGLAB toolbox. Statistical tests were performed on Python (3.11.5), using the SciPy package, except the mediation model, which was carried out on R (4.1.3) using the lavaan package.[42]

Data availability

The data used in this article is sensitive and abides by specific privacy regulations. Custom scripts used in this study are available upon reasonable request. Relevant code to replicate our analysis is available at http://www.georgnorthoff.com/code.

Results

Alpha and theta peaks in controls and DOC

The occurrence of a power peak in the alpha frequency range (7.5-13 Hz) is a common observation in the PSD of healthy subjects.[46] We started by determining whether we could replicate this finding in our control group (n = 25). Most subjects (frontal = 22; occipital = 22) exhibited a distinct peak in the frequency range between 7.5 and 13 Hz, with only 3 frontal channels subjects and 3 different occipital channels subjects not displaying any kind of peak.

Conversely, DOC patients show a decrease in alpha power and a shift to lower frequency bands, such as theta and delta.[12] We examined whether this pattern was reflected in our dataset and reproducible with our methodology. A Chi-Squared test compared controls and DOC patients on the observed occurrences of alpha peaks, theta peaks and no peaks (Table 1). Results proved to be statistically significant for both frontal, X^2 (2, N = 120) = 70.42, p < .001, and occipital electrodes, X^2 (2, N = 120) = 53.21, p < .001. Alpha peaks were significantly more prevalent in the control group compared to the DOC, which, in contrast, showed a higher incidence of theta peaks and 'flat' PSDs.

Table 1. Frontal electrodes: F1, FZ, F2. Occipital Electrodes: O1, OZ, O2

	N° of Recordings	Alpha Peak	Theta Peak	No Peak
Controls (frontal)	25	22 (88%)	0	3 (12%)
MCS (frontal)	48	3 (6.3%)	11 (22.9%)	34 (70.8%)
UWS (frontal)	47	4 (8.5%)	12 (25.5%)	31 (66%)
MCS + UWS (frontal)	95	7 (7.4%)	23 (24.2%)	65 (68.4%)
Controls (occipital)	25	22 (88%)	0	3 (12%)
MCS (occipital)	48	8 (16.7%)	11 (22.9%)	29 (60.4%)
UWS, (occipital)	47	5 (10.6%)	16 (34%)	26 (55.3%)
MCS + UWS (occipital)	95	13 (13.7%)	27 (28.4%)	55 (57.9%)

We then sought to determine whether our alpha peak measures would exhibit differences between controls and the few DOC patients who showed alpha peaks. We conducted Mann-Whitney U and independent t tests on 22 controls and 7 DOC for frontal electrodes, and 22 controls and 13 DOC for occipital electrodes. Overall, we found strong differences across six of our seven measures. Specifically, controls displayed higher *power*, *power ratio*, *frequency*, *prominence* and *minimum* *power*, while *maximum power* was higher in DOC, and *width* showed no statistically significant differences among the two groups. Results are summarized in Fig. 4.

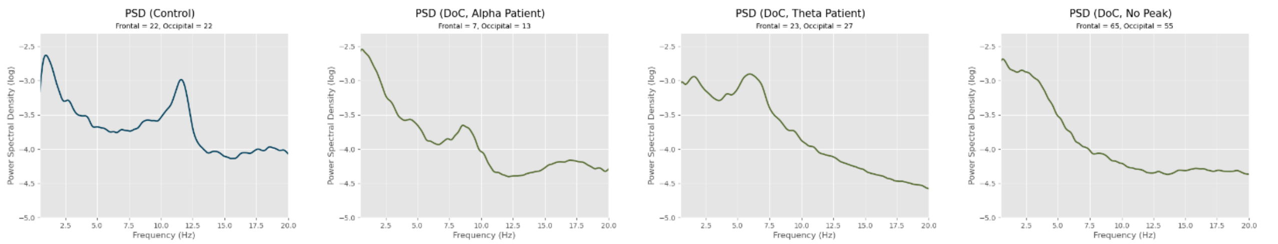

Figure 3 – Variations in Power Spectral Density.

Four distinct PSDs are displayed: a clear peak in the alpha range is visible for the healthy control (utmost left plot), which sees a considerable decrease in *power*, *prominence* and *frequency* in DOC patients (middle left plot), shifting to the theta range (middle right) or disappearing entirely (utmost right plot).

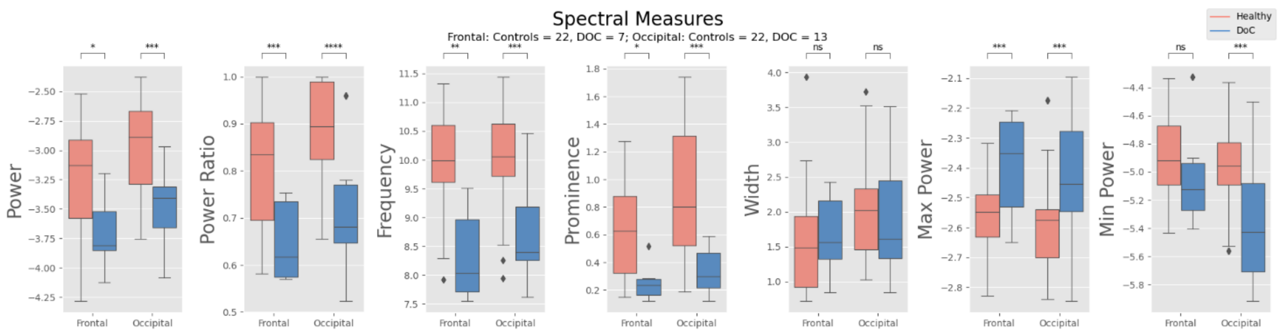

Figure 4 – Alpha spectral measures in controls and DOC patients.

Through peak analysis we identify seven spectral measures, five directly related to the alpha peak and two non-peak related. Controls exhibit higher values across almost all measures, except for *width* (showing no statistically significant differences) and *maximum power* (higher in DOC patients). Ns: $p \geq 0.05$; *: $0.01 < p < 0.05$; **: $0.001 < p < 0.01$; ***: $0.0001 < p < 0.001$; ****: $p \leq 0.0001$.

Autocorrelation window (ACW) in controls and DOC

ACW has been previously demonstrated to be prolonged in disorders of consciousness.[23,24] In this study, we replicate this finding by comparing the entire control group (n = 25) with the entire DOC group (n = 95) and extend it to different novel ACW measures (i.e. ACW-0, ACW e^{-1} and ACW-50). Mann-Whitney *U* tests demonstrated high statistical significance ($p < 0.001$). Figure 5b displays the results.

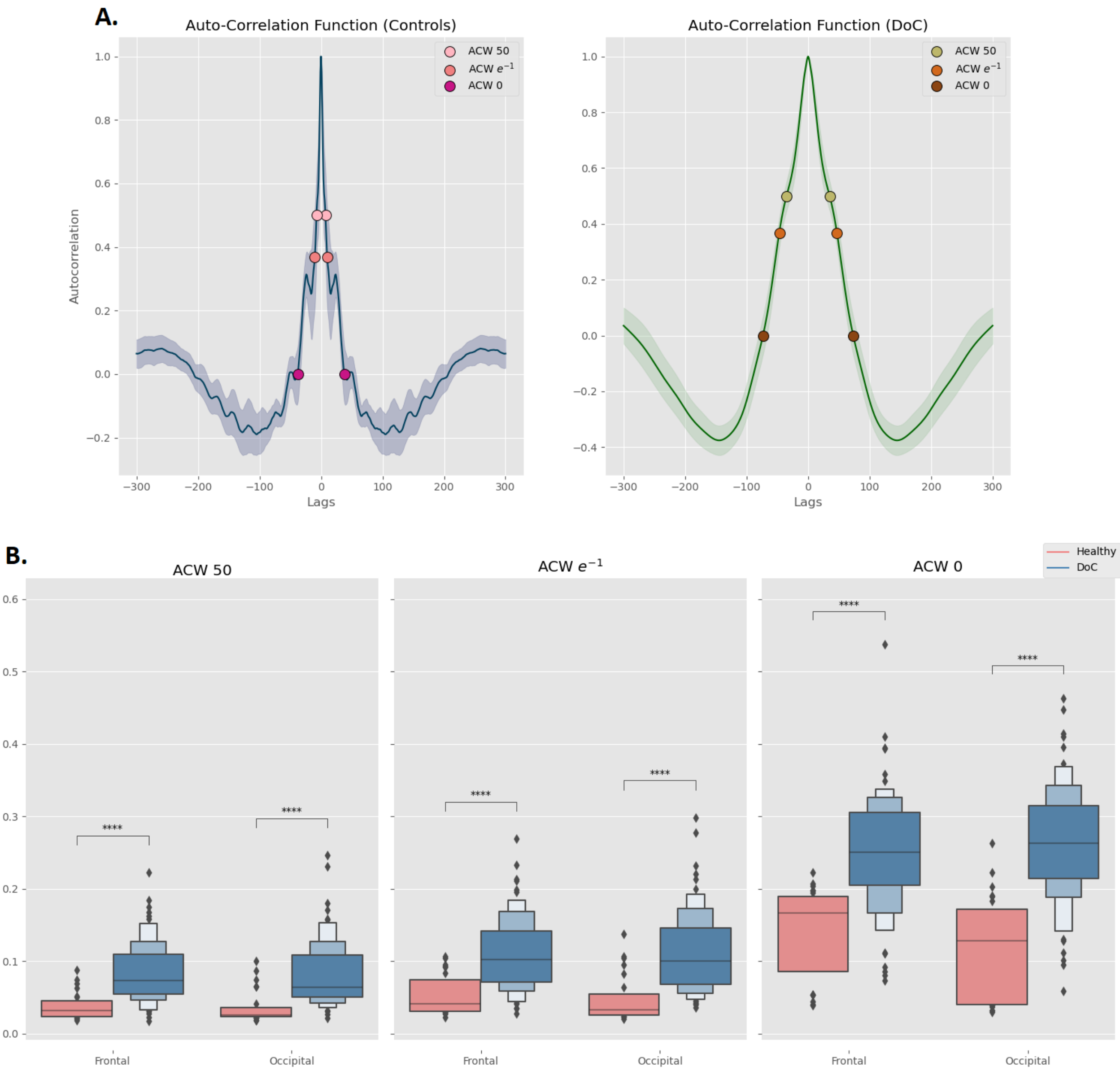

Figure 5. – ACW, controls and DOC.

Patients with disorders of consciousness exhibit prolonged ACW: this difference is clearly visible when comparing two Autocorrelation Functions side by side (a). In our study we replicate this finding and extend it to ACW-e^{-1} (b). *: $0.01 < p < 0.05$; **: $0.001 < p < 0.01$; ***: $0.0001 < p < 0.001$; ****: $p \leq 0.0001$.

Relationship between INTs and alpha peak

Given the observed differences of both INTs and alpha peaks in our DOC subjects, we focused on the potential link between the two.

Controls

We performed Pearson's and Spearman's correlations between ACW and spectral measures. Controls (frontal = 22, occipital = 22) displayed strong negative correlations for *power* and *power ratio*, while *maximum power* showed very strong positive correlations with ACW, reaching high levels of statistical significance. Among the other measures, *prominence*, *width* and *minimum power* showed weak to moderate negative correlations, without reaching statistical significance. For *frequency*, correlation coefficients were positive, but the level for statistical significance was not achieved.

DOC

We then conducted the same analysis on DOC subjects who displayed alpha peaks (frontal = 7; occipital = 13) and, afterwards, on those with a theta peak (frontal = 23; occipital = 27).

Overall, results appeared similar to the ones for controls, displaying moderate to strong negative correlations for *power*, *power ratio*, and very strong correlations for *maximum power*. Interestingly, correlation coefficients for *prominence* and *width* were positive, while controls had shown negative correlations for these measures. *Frequency* displayed weak to moderate correlations (e.g. $r = 0.58$ for ACW-0, in frontal electrodes), but none having p value $< .05$.

When shifting our focus on DOC patients displaying theta peaks (frontal = 23, occipital = 27), results closely resembled those described for alpha peak in DOC patients and controls, revealing strong and very strong negative correlations for *power* and *power ratio*, and positive correlations for *maximum power*, with *prominence*, *width* and *frequency* failing to reach statistical significance. Interestingly, correlation coefficients for *prominence* and *width* were negative, similar to controls but in contrast to alpha peak DOC subjects.

In summary, our results reveal strong negative correlations with ACW for *power* and *power ratio* and nearly perfect positive correlations for *maximum power*. *Prominence*, *width*, *frequency* and minimum power displayed weak to moderate correlations but did not reach significance level. Full results are presented in Figure 6.

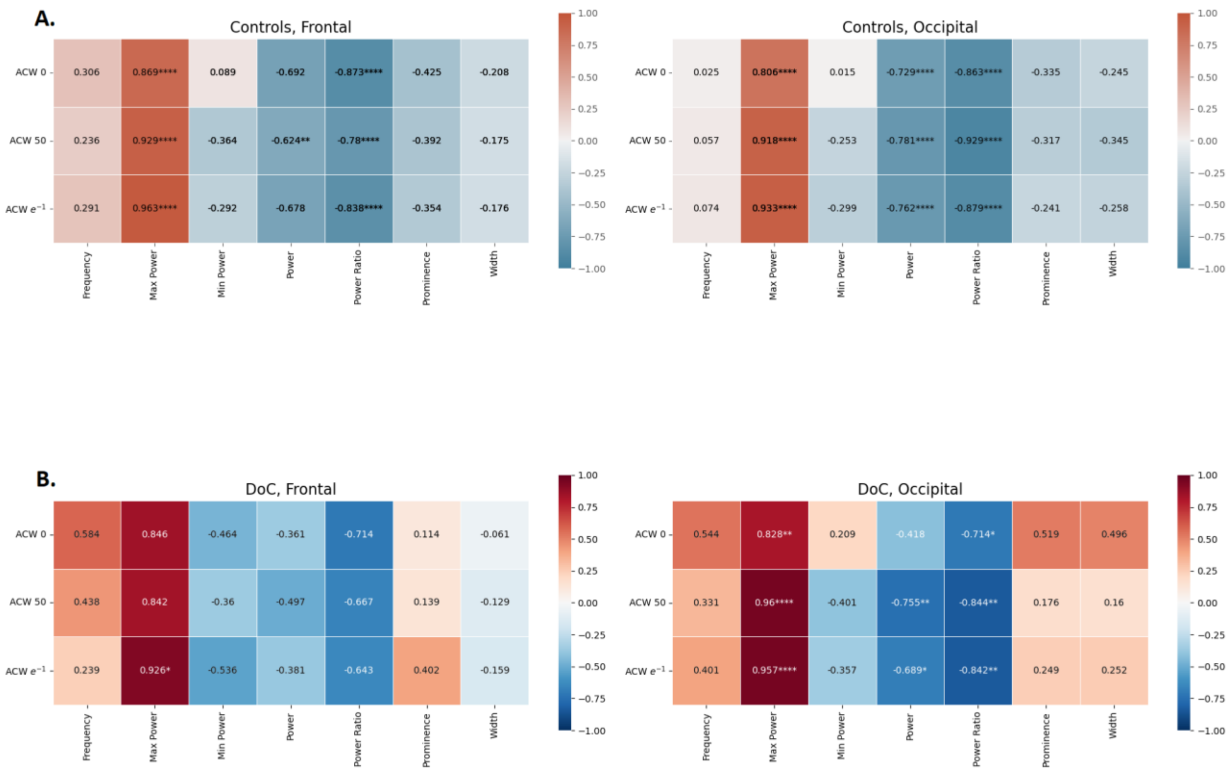

Figure 6 – Correlations between ACW and alpha spectral measures in controls and DOC.

ACW and alpha peak hold a strong relationship, especially for *power*, *power patio* and *maximum power*, which exhibit very strong correlations. These correlations are present both in healthy controls (a) and in DOC individuals (b). *: $0.01 < p < 0.05$; **: $0.001 < p < 0.01$; ***: $p < 0.001$.

INTs as mediator between theta peak and the state of consciousness

Next, our inquiry turned to the possible relationship between INTs and the state of consciousness as measured by the Coma Recovery Scale-Revised (CRS-R). Two significant negative correlations were found between ACW and CRS-R in DOC patients displaying theta peaks (frontal = 23, occipital = 27): ACW-e^{-1} ($r = -0.46$, $p = .025$) and ACW-0 ($r = -0.46$, $p = .025$) for occipital electrodes. However, no significant correlations were found in alpha peak DOC patients (frontal = 7, occipital = 13) or across the entire DOC group ($n = 95$). When turning our focus to potential links between spectral measures and CRS-R no significant correlations surfaced (Fig. 7A).

We contemplated the possibility of a link between the three elements and considering the above findings, we posited that ACW could serve as a mediator, with peak measurements acting as independent variables and CRS-R as the outcome. Given the low sample size of alpha peak patients, mediation models were attempted only for DOC subjects who displayed theta peaks. The variables used for the models were selected based on the correlational findings described above: ACW-e^{-1} and

ACW-50 had demonstrated significant correlations with CRS-R, while *power*, *power ratio* and *maximum power* had shown the strongest links to ACW. Two significant models were identified for occipital electrodes (n = 27), while no such results were found for frontal electrodes (n = 23). It is essential to approach these mediation results with caution due to the cross-sectional nature of the data and the low sample size.[47]

Figure 7b summarizes the results. The predictor variable for the first model was *power*, while ACW-e^{-1} served as the mediator. This model revealed an indirect effect of *power* on CRS-R (ab = 0.5, p = .006). The second model, using *power ratio* as the independent variable and ACW-e^{-1} as the mediator, also demonstrated an indirect effect of ab = 0.66, p = .0012.

Taken together, our findings indicate negative correlations between ACW and CRS-R in patients displaying theta peaks. Additionally, we identified two significant mediation models for theta peak subjects, where *power* or *power ratio* served as independent variables, ACW-e^{-1} acted as mediator and CRS-R as the outcome.

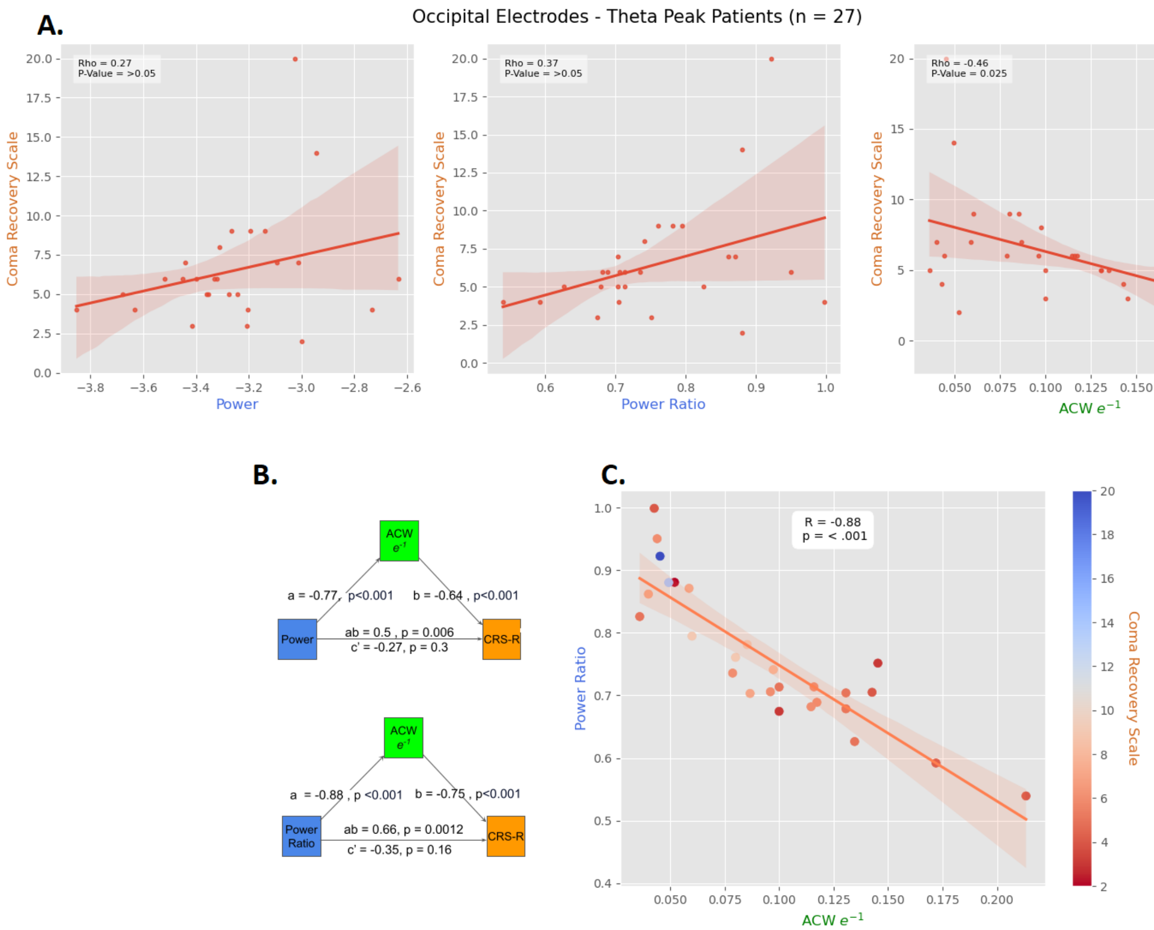

Figure 7 – Mediation analysis.

Our mediation analysis starts from observing strong correlations between ACW and peak measures (Fig. 6) and correlations between ACW and CRS-R, which in turn, are absent between peak and CRS-R (a). The mediation models (b) hint at ACW possibly serving as mediators between peak and CRS-R. Panel c displays the strong correlation between power ratio and ACW, with CRS-R showing a weak tendency to decrease as ACW increases.

INTs and peak measures sort according to the state of consciousness

Next, we aimed at classifying individual DOC patients into groups based on spectral measures and INTs. Initially, we sought to determine whether DOC patients with a spectral peak (frontal = 30; occipital = 40) exhibited differences in ACW compared to those without peaks (frontal = 65; occipital = 55). We categorized patients into two groups based on peak presence or absence and employed Mann Whitney *U* and independent t tests. Significant differences were identified for all three ACW measures, albeit exclusively in occipital electrodes. On average, patients with a theta peak displayed shorter ACW values, with the most significant difference being ACW-50 in occipital electrodes: median ACW-50 values in subjects with a peak and without a peak were 0.083 s and 0.059 s, respectively, (Mann-Whitney $U = 743$, $p = .022$; see Supplementary Figure 1).

Next, we split DOC subjects (n = 95) into three equal parts based on their ACW, identifying a group with low ACW, a group with intermediate ACW and a group with high ACW (see Fig. 8A). We then counted the presence and absence of peaks in each group. On average, patients with a longer ACW (i.e. ACWs in the top quantile) had fewer peaks (alpha or theta) across all ACW measures, except for ACW-0 in frontal electrodes, where the peak count was lowest for the middle quantile and intermediate for the top quantile. A Chi Squared test yielded only one significant result: ACW-0 in the occipital group, X^2 (2, $N = 95$) = 10.9, $p = .013$.

We additionally performed a median split analysis, which included DOC patients exhibiting a peak (alpha or theta) in occipital electrodes (n = 40). The median split was performed based on ACW-e^{-1}, and variables that had shown statistically significant results in the mediation model (*power*, *power ratio* and CRS-R) were separated according to the split. Independent t tests revealed that subjects in the top ACW quantile (*power*: M = -3.48, SD = 0.23), displayed lower *power* than subjects in the bottom quantile (M =-3.18m SD = 0.26), $t(38) = 3.89$, p <.001. Similarly, for *power ratio*: top quantile (M = 0.66, STD = 0.064) and bottom quantile (M = 0.82, STD = 0.092) displayed statistically significant differences, with the top quantile having a lower *power ratio*, $t(38) = 3.89$, p <.001. CRS-R also exhibited significant differences between the top quantile (median = 5) and the bottom quantile (median = 7), Mann-Whitney $U = 284$, $p = .022$. In contrast to median splits based on ACW, no statistically significant differences for CRS-R were found when attempting splits based on *power* or *power ratio* (Fig. 8B). This suggests a special role of ACW in sorting and distinguishing individual DOC patients with respect to their state of consciousness.

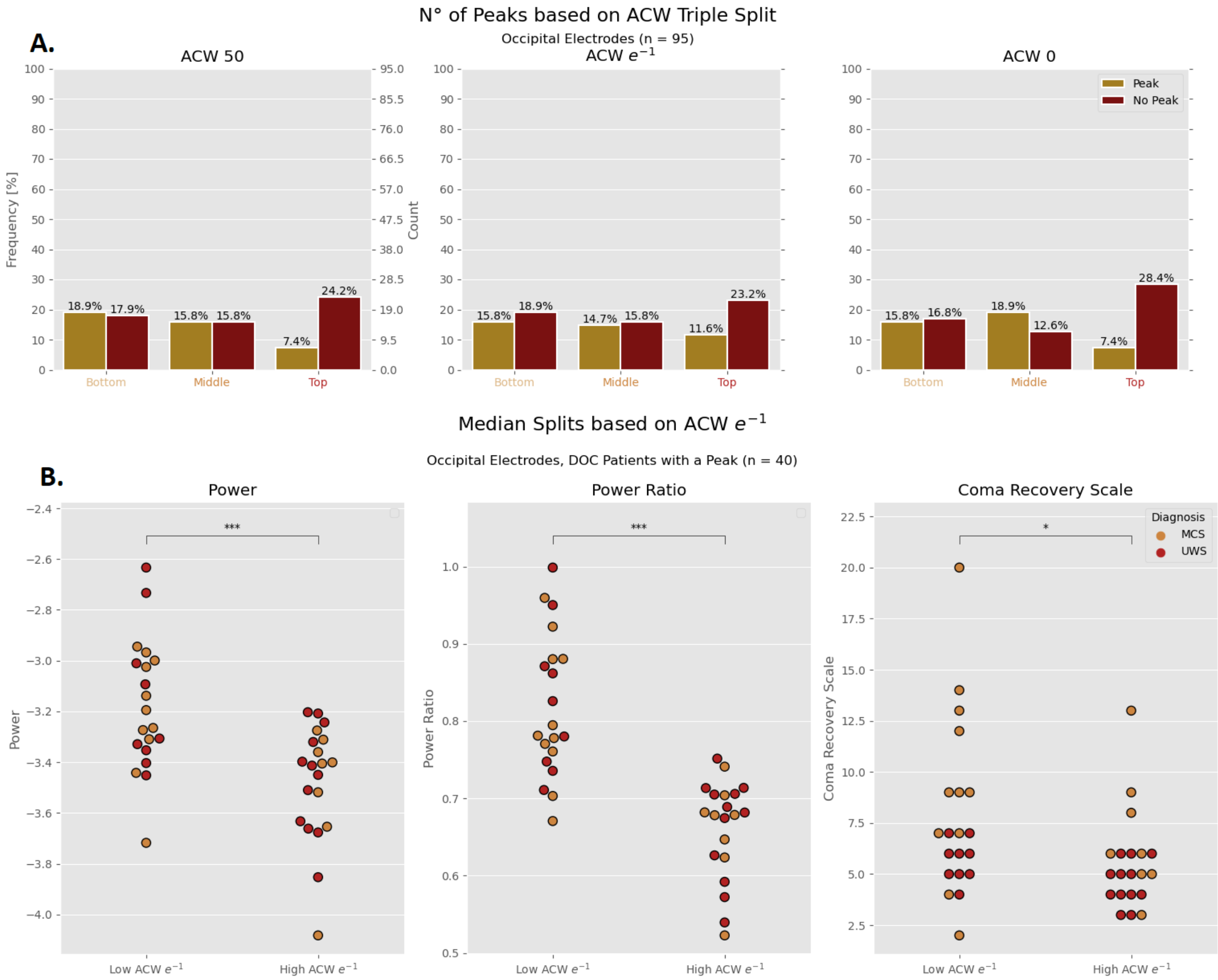

Figure 8 – ACW splits.

The link between ACW and spectral peaks in DOC subjects extends from the weakening to the disappearance of all spectral peaks: patients in the top quantile for ACW length possess, on average, a lower chance of displaying a spectral peak (a). ACW allows segregation of peak measures and CRS-R (b). Ns: $p \geq 0.05$; *: $0.01 < p < 0.05$; **: $0.001 < p < 0.01$; ***: $0.0001 < p < 0.001$; ****: $p \leq 0.0001$.

Taken together, we show that DOC patients who exhibit a spectral peak (either in the alpha or theta frequency ranges) tend to have a shorter ACW. Secondly, DOC subjects with a prolonged ACW less commonly exhibit spectral peaks. Thirdly, DOC individuals with longer ACW-e^{-1} tend to have lower CRS-R scores. In summary, we provide compelling evidence for a link between ACW, spectral peaks and the state of consciousness, with ACW potentially serving as a central component in this intricate relationship.

Alpha peak and INTs for classifying the state of consciousness

Next, we aimed at exploring whether the conjoint use of ACW and spectral measures would allow the classification of subjects based on their state of consciousness. Employing an SVM model, our objective was to classify subjects into two categories initially (controls and DOCs), followed by three categories (controls, MCS and UWS). For this analysis, we aggregated data obtained from both frontal and occipital channels. Only datapoints related to alpha peaks were utilized, given that no healthy subjects presented theta peaks. Consequently, the dataset comprised 44 healthy controls (22 frontal and 22 occipital) and 20 DOC subjects (7 frontal and 13 occipital). Three models were employed for each classification task: one utilizing only alpha peak features, a second using solely ACW features and finally, one combining both alpha and ACW features.

	Accuracy	Precision	Recall	F1 Score	AUC
Alpha Features only	93.6% (±8.3%)	90.5% (±12.4%)	100% (±0%)	94.6% (±7%)	86.7% (±31.2%)
ACW Features only	90.5% (±11.4%)	88.3% (±17.7%)	98 (±6.3%)	91.7% (±11.1%)	82.8% (±34.6%)
Alpha and ACW Features	95.5% (±7.3%)	95.5% (±9.6%)	98.6% (±4.5%)	96.7% (±5.6%)	88.9% (±31.4%)

Table 2 – Results for Healthy-DOC classification problem across 10 folds.

The alpha peak – ACW SVM model displays high performance in classifying controls and DOC.

For our initial classification task (Controls vs. DOC), all models demonstrated high accuracy (see Table 2). Specifically, the alpha peak-only model achieved 93.57% (± 8.33%) accuracy, the ACW-only model achieved 90.48% (± 11.39%) accuracy, while the combined alpha peak and ACW model attained the highest accuracy of the three (95.48 ± 7.31%). Similarly, precision, recall, F1 score, and AUC yielded very high values. For our second classification task (Controls vs. MCS vs. UWS), accuracy witnessed a notable drop across all three models: the alpha peak-only model achieved 77.62% (± 9.47%) accuracy, the ACW-only model attained the highest accuracy (79.52% ± 13.05%), while the conjoint model achieved 78.33% ± 12.57% accuracy. Overall, precision, recall, F1 score, and AUC remained high, ranging from 90 to 95% (see Supplementary Table 1 for complete results). It is worth noting, though, that these metrics are largely influenced by the number of true positives. Indeed, as depicted in Supplementary Figure 5, the combined alpha peak-ACW model achieved nearly perfect classification of healthy subjects into their respective category (misclassifying only 3 out of 44 healthy individuals out as MCS, and thus resulting in a high true positive rate). However, the model encountered difficulty in distinguishing between MCS and UWS, correctly classifying only 6 out of 15 MCS and 3 out 5 UWS subjects, leading to higher misclassification rates.

In summary, our machine learning analysis demonstrates that alpha peak spectral measures and ACW are effective in discriminating between healthy controls and DOC individuals. However, their utility in distinguishing between MCS and UWS remains limited.

Discussion

In the present study, we tackle one of the most consistent observations in the resting state EEG of patients with disorders of consciousness: the decrease in power in the alpha range compared to healthy controls. We approach this finding as a weakening or disappearance of the alpha peak and exploit it for the clinical diagnosis of the state of consciousness in DOC subjects. We perform a peak analysis on the PSD and measure INTs (probed through ACW) from EEG signals obtained from twenty-five healthy controls and eight-eight DOC patients.

Quantifying the weakening of the alpha peak in DOC

A decrease in resting-state power in the alpha band consistent with a decrease in the state of consciousness has already been reported.[9,12,16,17] We extended this finding by employing peak-analysis aimed at specifically quantifying not only the decline in power, but also the weakening of the alpha peak in its characteristics (i.e. peak-related measures). Alpha peak measures show significant decreases in DOC individuals across almost all measures in both frontal and occipital electrodes, with the only exception being *maximum power* (which shows an increase in DOC subjects) and *width*. Additionally, we note the shifting of the alpha peak to the theta band in several DOC individuals. This phenomenon has been reported in MCS subjects[29] and has also been observed in healthy subjects under the influence of ketamine.[6,30,31] Importantly, patients administered with ketamine report dream-like experiences upon emergence from anesthesia[48] indicating the presence of consciousness and opening up the question of whether patients in MCS could share a similar experience. Further research should aim to replicate these findings and explore whether a peak in power in the theta band could potentially serve as an indirect correlate of a reduced/altered, yet present, state of consciousness.

Regarding *maximum power*, multiple studies have linked high amplitude of delta waves to states of reduced or loss of consciousness, such as deep sleep[23,49,50] and anesthesia.[23,49,51] Further, an increase in delta power has been demonstrated as a consistent finding in patients with disorders of consciousness.[9,12,14,16,17,23] While "*maximum power*" in our measurement of alpha or theta peak does not necessarily correspond to the maximum power in the delta band itself, it is worth noting that the

PSD for EEG signals generally exhibits an inverse exponential trend, placing *maximum power* almost invariably in the delta range. With this limitation in mind and considering the different methodology employed in our study, we indirectly replicate the finding of increased delta power in DOC patients.

Prolongation of INTs mediates the impact of theta peak on the level of consciousness

First, we replicate the finding of prolonged INTs in DOC patients with respect to control individuals.[23,24,49] Our study replicates and extends previous results through the inclusion of ACW-e^{-1} and adds to the growing body of literature on INTs and their relation to consciousness, neurological and mental disorders.[52–57]

The negative correlations between our peak measures and ACW indicate that the weakening of both alpha and theta peak is strongly related to prolongation of the INTs. Moreover, controls and patients with absence of a spectral peak exhibit a longer ACW (see Supplementary Figures 2 and 3), which further extends the relation between spectral peaks and INTs along the continuum from the weakening of alpha and theta peaks to their disappearance. These results appear robust, with correlations applying both to controls and DOC patients.

In our study, we find weak-to-moderate correlations between ACW and CRS-R in occipital electrodes for subjects displaying a theta peak ($n = 27$). , The mediation analysis pointed at the possible explanation of INTs as mediator in the relationship between theta peaks and the level of consciousness (i.e. CRS-R).

On a related note, previous research has found that some healthy subjects may demonstrate low amplitude or no alpha peak, a phenotype known as Low-Voltage EEG (LVEEG).[58] LVEEG has an elusive definition, with some studies defining it as a low voltage across the whole frequency spectrum[59] and others restricting their definition specifically to the alpha band.[60] Bazanova and colleagues[58] report a prevalence ranging between 3 and 13% in healthy adults, in line with our findings (i.e. 12%). Given our correlational findings, we suggest, albeit tentatively, that LVEEG may be related to longer INTs in these healthy subjects. However, this remains to be further tested in the future.

Peak analysis and INTs as potential markers for the state of consciousness

The correlations observed between ACW and CRS-R, coupled with our mediation analysis findings, suggest the possibility of utilizing our spectral measures and ACW as markers for the state of consciousness. This possibility was first explored through split analyses, demonstrating that the conjoined ACW and peak measures yielded good discrimination between controls and DOC. This, in turn, guided our machine learning analyses, which demonstrated high accuracy (95.5%) for the combined alpha peak-ACW model in discriminating controls from DOC subjects, indicating that the weakening, shifting to the theta range and, ultimately, the disappearance of the alpha peak might possess important information for assessing the state of consciousness.

While further research is needed, the use of peak analysis and ACW could potentially serve as a relatively straightforward method for clinicians to obtain a preliminary assessment of a patient's consciousness state through a quick glance at a PSD or at an Autocorrelation Function (ACF) graph. Indeed, the pronounced differences in our measures between controls and DOC individuals are readily apparent upon visual inspection (e.g., see Figure 3 for a comparison of PSDs between healthy controls and DOC patients, and Figure 5A for two ACF graphs depicting healthy and DOC individuals). However, our machine learning results suggest that our measures currently lack the precision required for a more fine-grained clinical distinction of the state of consciousness, such as discriminating between MCS and UWS.

However, as demonstrated in previous machine learning studies,[9,16] optimal outcomes in classifying subjects based on their state of consciousness are achieved when combining EEG markers of diverse natures: each marker serving a unique role, with some excelling in discriminating controls and UWS, while others in distinguishing between MCS and UWS, and so forth. For instance, ACW and Peak analysis measures, by effectively differentiating healthy individuals from DOC, may aid in bridging the gap between behavior and consciousness by identifying cases of Cognitive Motor Dissociation (CMD).[61–63] Further validation is needed to determine whether more fine-grained measures of ACW and spectral peak analysis could allow for an accurate distinction between MCS and UWS.

Limitations

Important limitations regarded the sample size, which for most of our analyses was low (especially for mediation analysis, which requires longitudinal data and large sample sizes to obtain reliable results),[47] a direct consequence of the fact that most DOC patients did not show any spectral peaks in the frequency bands of interest. Indeed, our approach through peak analysis here exhibits its greatest weakness, that is, not being applicable to all participants.

Additionally, multiple factors are known to influence alpha band amplitude, such as, for example, cerebral blood flow (with power increasing as blood flow increases).[66] Importantly, suppression of the alpha band waves is obtained upon eye-opening, a phenomenon known as the Berger effect.[67] Indeed, these possible confounding factors were not accounted for in our research, with half of our patients being affected by stroke (and therefore likely having significantly impaired or altered cerebral blood flow) and whether DOC patients had their eyes opened or closed at the moment of recording was not documented.

Furthermore, research on quantitative EEG undermines the idea of alpha power being specifically linked to the state of consciousness. Some studies have found a decreased relative alpha power in subjects with mild traumatic brain injury (the second most common cause of DOC in our dataset),[68] while a lower relative alpha power appears to be a key prognostic marker in stroke patients[69] (stroke being the leading cause of DOC in our dataset). A recent study conducted by Colombo and colleagues[15] has found that a decrease in alpha power could discriminate exclusively between anoxia and non-anoxia DOC individuals, but not between conscious and unconscious subjects. The authors concluded that alpha power suppression might indicate widespread cortical damage, rather than carrying specific information about the state of consciousness. Indeed, the studies referenced in this paragraph, along with recent research,[70] highlight the crucial role of etiology in Disorders of Consciousness, identifying it as a major confounding factor in the search for markers for consciousness.

Finally, our study, like many others investigating markers for the state of consciousness, measures the validity of its proposed markers using the CRS-R as benchmark – the same scale that researchers seek to overcome. This presents a complex epistemological challenge[71] that we acknowledge, although we do not intend to tackle.

Conclusion

Building upon existing literature, we emphasize the connection between the decrease in power within the alpha band and the level or state of consciousness—a relationship that remains to be fully understood. Through peak analysis, we developed novel measures to quantify and measure the alpha peak itself, and showed its weakening, shift to theta peak, and/or complete disappearance in the resting state EEG of patients with DOC. This was accompanied by prolongation of INTs, as measured through ACW, which correlates with standardized behavioral assessment of consciousness (i.e. CRS-R) in DOC subjects. Mediation analysis hinted at the possibility of ACW mediating the relationship of alpha/theta peak with the level of consciousness. Finally, through data sorting with split analyses and machine learning, we demonstrate that the conjoint measures of both alpha peak and INTs can effectively differentiate controls and DOC individuals with high accuracy. In conclusion, we highlight the intricate relationship between alpha/theta peaks, ACW and the state of consciousness (i.e. CRS-R) which, tentatively, lays the groundwork for future research aimed at exploring these measures as potential clinical biomarkers of the level or state of consciousness.

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Competing interests

The authors report no competing interests.

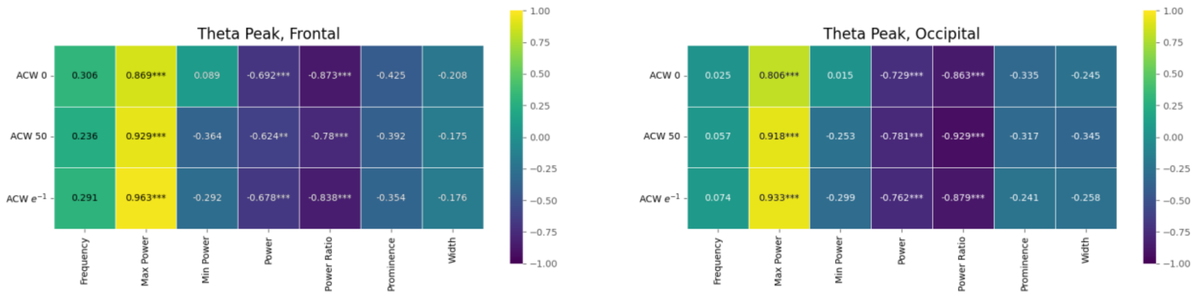
Supplementary material

Modulating peak analysis

To modulate the analysis, the “findpeaks” function provides the option to apply various thresholds to exclude undesired peaks from the output. One such threshold is the ‘minimum peak width’, which can be set to exclude peaks with widths below the specified threshold from the function’s output. The only thresholds used in our analysis were: minimum distance between peaks (set to 0.4 in our study) and minimum peak prominence (set to 0.1 in our study). The values just noted, and the values obtained for the spectral measures previously described, are expressed as units of X and Y coordinates, respectively. As an example, a peak whose *width* ranges from $x_1 = 9$ to $x_2 = 11$ will have a *width* of $|x_2| - |x_1| = 2$; a peak whose *power* is $y_1 = -3.2$ and highest minimum is $y_2 = -3.7$ (in logarithmic scale) will have a *prominence* of $|y_2| - |y_1| = 0.5$. Units for the X-axis measures (i.e. *width* and *frequency*) are therefore expressed in Hz, whereas units for the Y-axis measures (*power*, *prominence*, *maximum mower*, and m*inimum power*) are in the unit of power.

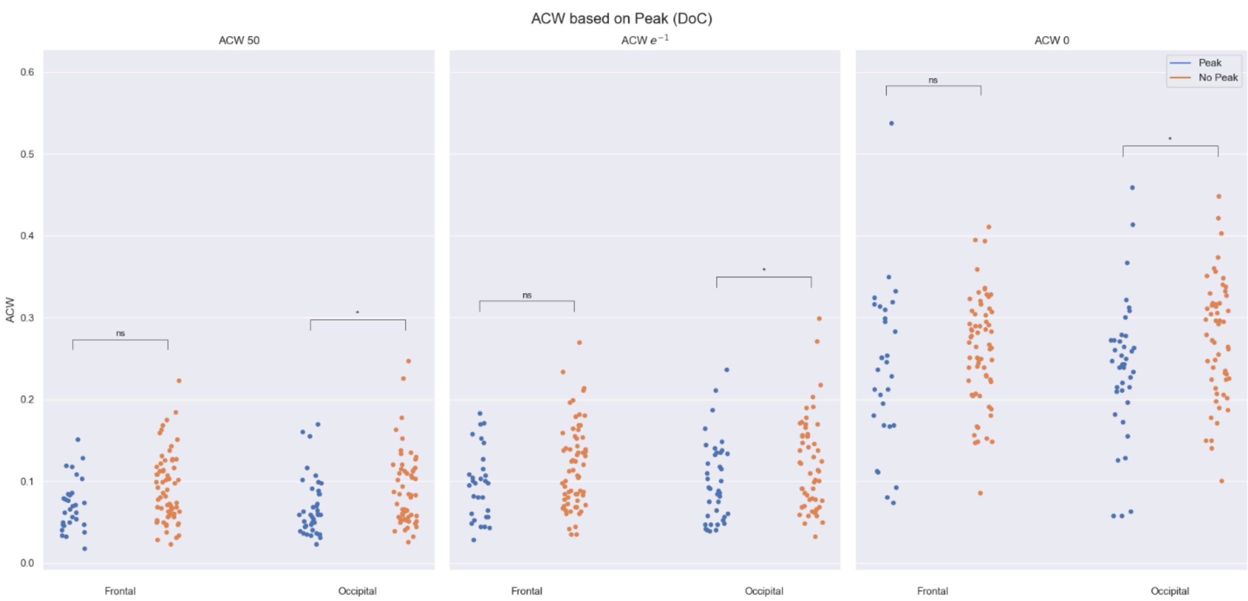
We additionally note that the analysis was performed on the PSD with power set to logarithmic scale in base 10, a commonly used way to visualize power spectral graphs. The function returns the PSD graph with the identified peaks annotated, and all graphs (both frontal and occipital) were visually inspected.

Supplementary figures



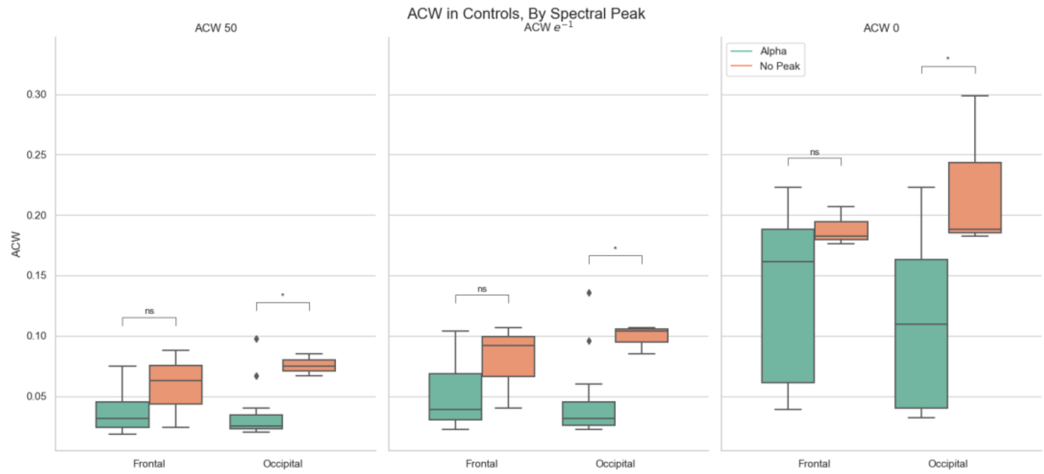
Supplementary figure 1 – Correlations between ACW and alpha spectral measures.

Correlations between ACW and alpha spectral measures (both in controls and in DOC) are present in theta peak DOC individuals too.



Supplementary figure 2 – ACW in patients with and without a peak.

DOC patients with a peak appear to have a shorter ACW, on average. However, only occipital electrodes reveal statistically significant differences.



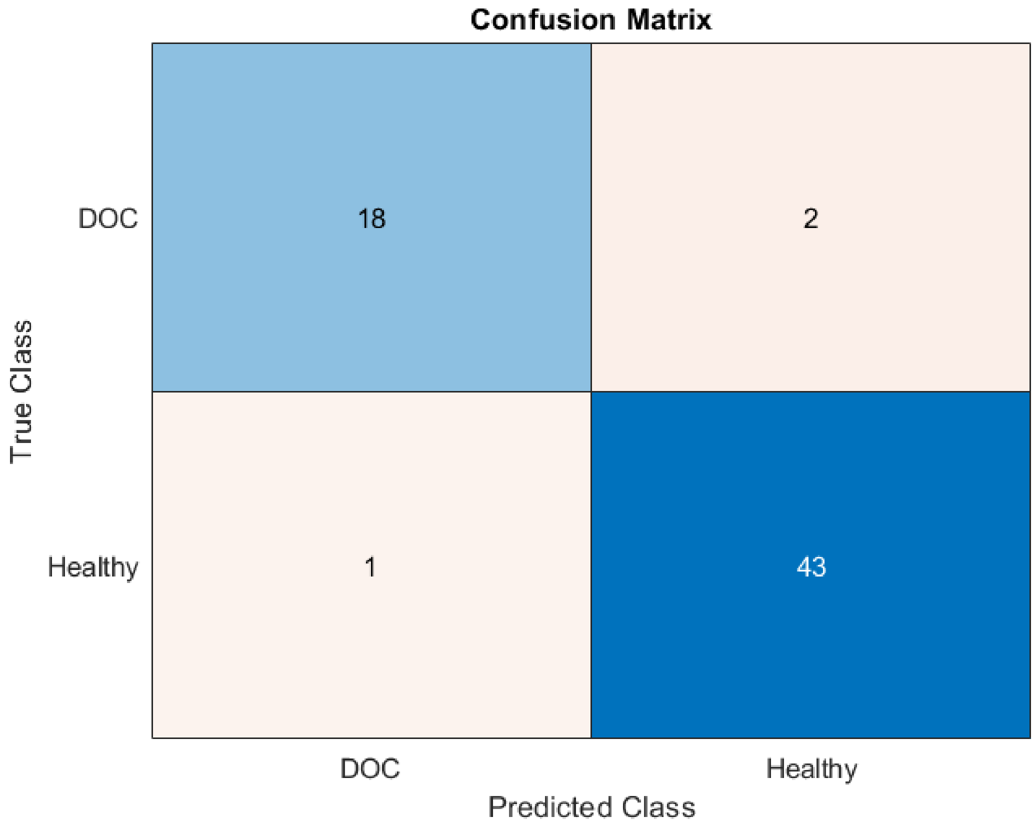
Supplementary figure 3 – ACW in healthy controls with and without a peak.

Similarly to DOC patients, controls without a peak appear to exhibit a longer ACW. Given the scarce number of subjects without a peak in the control group (frontal = 3, occipital = 3) results should be interpreted with caution.

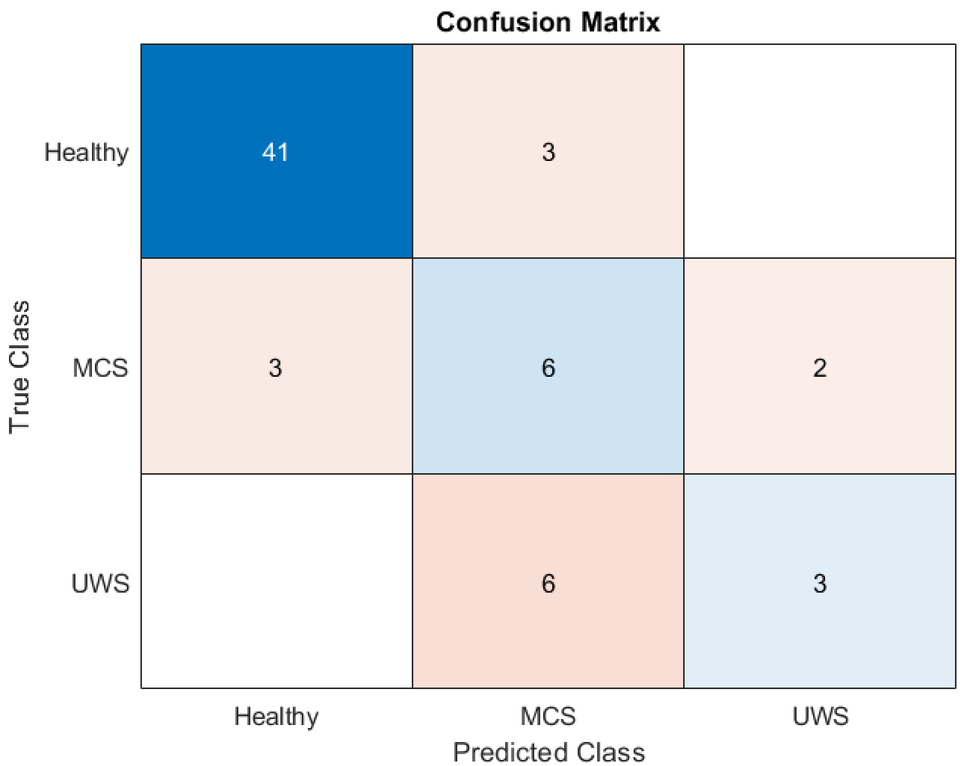
	Accuracy	Precision	Recall	F1 Score	AUC
Alpha Features only	77.6% (±9.5%)	92.3% (±9.9%)	100% (±0%)	95.8% (±5.5%)	90% (±31.6%)
ACW Features only	79.5% (±13.1%)	89% (±12.4%)	98 (±6.3%)	92.9% (±8.3%)	86.5% (±31.5%)
Alpha and ACW Features	78.3% (±12.6%)	94.3% (±9.2%)	94% (±13.5%)	93.3% (±8.3%)	90% (±31.6%)

Supplementary table 1 – Results for healthy-MCS-UWS classification problem across 10 folds.

The table presents the results for our second classification problem, utilizing the combined alpha peak – ACW SVM model. Overall, we notice a sharp decrease in accuracy, while other measures of performance remain high – likely a correlate of a high accuracy in classifying healthy controls.



Supplementary figure 4 – Confusion Matrix for the combined alpha peak-ACW SVM model, classifying Healthy Controls vs. DOC subjects.



Supplementary figure 5 – Confusion matrix for healthy-MCS-UWS classification problem.

The alpha peak-ACW SVM model correctly identifies healthy controls with extremely high accuracy. However, spectral measures and ACW do not appear to hold relevant information for distinguishing between MCS and UWS.

References

1. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. 2004;85(12):2020-2029. doi:10.1016/j.apmr.2004.02.033

2. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. *Nat Rev Neurol*. 2014;10(2):99-114. doi:10.1038/nrneurol.2013.279

3. Wang J, Hu X, Hu Z, Sun Z, Laureys S, Di H. The misdiagnosis of prolonged disorders of consciousness by a clinical consensus compared with repeated coma-recovery scale-revised assessment. *BMC Neurol*. 2020;20:343. doi:10.1186/s12883-020-01924-9

4. Casali AG, Gosseries O, Rosanova M, et al. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med*. 2013;5(198):198ra105. doi:10.1126/scitranslmed.3006294

5. Sinitsyn DO, Poydasheva AG, Bakulin IS, et al. Detecting the Potential for Consciousness in Unresponsive Patients Using the Perturbational Complexity Index. *Brain Sci*. 2020;10(12):917. doi:10.3390/brainsci10120917

6. Zilio F, Gomez-Pilar J, Chaudhary U, et al. Altered brain dynamics index levels of arousal in complete locked-in syndrome. *Commun Biol*. 2023;6(1):1-19. doi:10.1038/s42003-023-05109-1

7. Liu Y, Zeng W, Pan N, Xia X, Huang Y, He J. EEG complexity correlates with residual consciousness level of disorders of consciousness. *BMC Neurol*. 2023;23(1):140. doi:10.1186/s12883-023-03167-w

8. Bodart O, Gosseries O, Wannez S, et al. Measures of metabolism and complexity in the brain of patients with disorders of consciousness. *NeuroImage Clin*. 2017;14:354-362. doi:10.1016/j.nicl.2017.02.002

9. Sitt JD, King JR, El Karoui I, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain J Neurol*. 2014;137(Pt 8):2258-2270. doi:10.1093/brain/awu141

10. Hermann B, Stender J, Habert MO, et al. Multimodal FDG-PET and EEG assessment improves diagnosis and prognostication of disorders of consciousness. *NeuroImage Clin*. 2021;30:102601. doi:10.1016/j.nicl.2021.102601

11. Pruvost-Robieux E, Marchi A, Martinelli I, Bouchereau E, Gavaret M. Evoked and Event-Related Potentials as Biomarkers of Consciousness State and Recovery. *J Clin Neurophysiol*. 2022;39(1):22-31. doi:10.1097/WNP.0000000000000762

12. Lechinger J, Bothe K, Pichler G, et al. CRS-R score in disorders of consciousness is strongly related to spectral EEG at rest. *J Neurol*. 2013;260(9):2348-2356. doi:10.1007/s00415-013-6982-3

13. Goldfine AM, Victor JD, Conte MM, Bardin JC, Schiff ND. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2011;122(11):2157-2168. doi:10.1016/j.clinph.2011.03.022

14. Chennu S, Finoia P, Kamau E, et al. Spectral Signatures of Reorganised Brain Networks in Disorders of Consciousness. *PLOS Comput Biol*. 2014;10(10):e1003887. doi:10.1371/journal.pcbi.1003887

15. Colombo MA, Comanducci A, Casarotto S, et al. Beyond alpha power: EEG spatial and spectral gradients robustly stratify disorders of consciousness. *Cereb Cortex N Y NY*. 2023;33(11):7193-7210. doi:10.1093/cercor/bhad031

16. Engemann DA, Raimondo F, King JR, et al. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. *Brain J Neurol*. 2018;141(11):3179-3192. doi:10.1093/brain/awy251

17. Rossi Sebastiano D, Panzica F, Visani E, et al. Significance of multiple neurophysiological measures in patients with chronic disorders of consciousness. *Clin Neurophysiol Off J Int Fed Clin Neurophysiol*. 2015;126(3):558-564. doi:10.1016/j.clinph.2014.07.004

18. Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Rev*. 1999;29(2):169-195. doi:10.1016/S0165-0173(98)00056-3

19. Klimesch W. EEG-alpha rhythms and memory processes. *Int J Psychophysiol Off J Int Organ Psychophysiol*. 1997;26(1-3):319-340. doi:10.1016/s0167-8760(97)00773-3

20. Hasson U, Yang E, Vallines I, Heeger DJ, Rubin N. A hierarchy of temporal receptive windows in human cortex. *J Neurosci Off J Soc Neurosci*. 2008;28(10):2539-2550. doi:10.1523/JNEUROSCI.5487-07.2008

21. Murray JD, Bernacchia A, Freedman DJ, et al. A hierarchy of intrinsic timescales across primate cortex. *Nat Neurosci*. 2014;17(12):1661-1663. doi:10.1038/nn.3862

22. Wasmuht DF, Spaak E, Buschman TJ, Miller EK, Stokes MG. Intrinsic neuronal dynamics predict distinct functional roles during working memory. *Nat Commun*. 2018;9(1):3499. doi:10.1038/s41467-018-05961-4

23. Zilio F, Gomez-Pilar J, Cao S, et al. Are intrinsic neural timescales related to sensory processing? Evidence from abnormal behavioral states. *NeuroImage*. 2021;226:117579. doi:10.1016/j.neuroimage.2020.117579

24. Buccellato A, Zang D, Zilio F, et al. Disrupted relationship between intrinsic neural timescales and alpha peak frequency during unconscious states - A high-density EEG study. *NeuroImage*. 2023;265:119802. doi:10.1016/j.neuroimage.2022.119802

25. Golesorkhi M, Gomez-Pilar J, Tumati S, Fraser M, Northoff G. Temporal hierarchy of intrinsic neural timescales converges with spatial core-periphery organization. *Commun Biol*. 2021;4(1):1-14. doi:10.1038/s42003-021-01785-z

26. Wolff A, Di Giovanni DA, Gómez-Pilar J, et al. The temporal signature of self: Temporal measures of resting-state EEG predict self-consciousness. *Hum Brain Mapp*. 2019;40(3):789-803. doi:10.1002/hbm.24412

27. Honey CJ, Thesen T, Donner TH, et al. Slow cortical dynamics and the accumulation of information over long timescales. *Neuron*. 2012;76(2):423-434. doi:10.1016/j.neuron.2012.08.011

28. Wolff A, Berberian N, Golesorkhi M, Gomez-Pilar J, Zilio F, Northoff G. Intrinsic neural timescales: temporal integration and segregation. *Trends Cogn Sci*. 2022;26(2):159-173. doi:10.1016/j.tics.2021.11.007

29. Schiff ND, Nauvel T, Victor JD. Large-scale brain dynamics in disorders of consciousness. *Curr Opin Neurobiol*. 2014;25:7-14. doi:10.1016/j.conb.2013.10.007

30. Waschke L, Donoghue T, Fiedler L, et al. Modality-specific tracking of attention and sensory statistics in the human electrophysiological spectral exponent. Chait M, Shinn-Cunningham BG, Postle BR, Simon JZ, eds. *eLife*. 2021;10:e70068. doi:10.7554/eLife.70068

31. Colombo MA, Napolitani M, Boly M, et al. The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. *NeuroImage*. 2019;189:631-644. doi:10.1016/j.neuroimage.2019.01.024

32. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet Lond Engl*. 1974;2(7872):81-84. doi:10.1016/s0140-6736(74)91639-0

33. Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods*. 2004;134(1):9-21. doi:10.1016/j.jneumeth.2003.10.009

34. Liu Y, Li Z, Bai Y. Frontal and parietal lobes play crucial roles in understanding the disorder of consciousness: A perspective from electroencephalogram studies. *Front Neurosci*. 2023;16. doi:10.3389/fnins.2022.1024278

35. Piarulli A, Bergamasco M, Thibaut A, Cologan V, Gosseries O, Laureys S. EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness. *J Neurol*. 2016;263(9):1746-1760. doi:10.1007/s00415-016-8196-y

36. Naro A, Bramanti A, Leo A, et al. Shedding new light on disorders of consciousness diagnosis: The dynamic functional connectivity. *Cortex*. 2018;103:316-328. doi:10.1016/j.cortex.2018.03.029

37. Lubenchenko AV, Ivanov DA, Lukiantsev DS. Application of MatLab for Processing X-ray Photoelectron Spectroscopy Spectra. In: *2020 V International Conference on Information Technologies in Engineering Education (Inforino)*. ; 2020:1-4. doi:10.1109/Inforino48376.2020.9111800

38. Pham MH, Elshehabi M, Haertner L, et al. Validation of a Step Detection Algorithm during Straight Walking and Turning in Patients with Parkinson’s Disease and Older Adults Using an

Inertial Measurement Unit at the Lower Back. *Front Neurol*. 2017;8:457. doi:10.3389/fneur.2017.00457

39. Scally B, Burke MR, Bunce D, Delvenne JF. Resting-state EEG power and connectivity are associated with alpha peak frequency slowing in healthy aging. *Neurobiol Aging*. 2018;71:149-155. doi:10.1016/j.neurobiolaging.2018.07.004

40. Rodriguez-Larios J, Alaerts K. EEG alpha-theta dynamics during mind wandering in the context of breath focus meditation: An experience sampling approach with novice meditation practitioners. *Eur J Neurosci*. 2021;53(6):1855-1868. doi:10.1111/ejn.15073

41. Bassingthwaighte JB, Liebovitch LS, West BJ. *Fractal Physiology*. Oxford University Press; 1994. doi:10.1093/oso/9780195080131.001.0001

42. Rosseel Y. lavaan: An R Package for Structural Equation Modeling. *J Stat Softw*. 2012;48:1-36. doi:10.18637/jss.v048.i02

43. Rathgamage Don DP. Multiclass Classification Using Support Vector Machines. *Electron Theses Diss*. Published online January 1, 2018. https://digitalcommons.georgiasouthern.edu/etd/1845

44. Escalera S, Pujol O, Radeva P. On the Decoding Process in Ternary Error-Correcting Output Codes. *IEEE Trans Pattern Anal Mach Intell*. 2010;32:120-134. doi:10.1109/TPAMI.2008.266

45. Escalera S, Pujol O, Radeva P. Separability of ternary codes for sparse designs of error-correcting output codes. *Pattern Recognit Lett*. 2009;30(3):285-297. doi:10.1016/j.patrec.2008.10.002

46. Başar E. A review of alpha activity in integrative brain function: Fundamental physiology, sensory coding, cognition and pathology. *Int J Psychophysiol*. 2012;86(1):1-24. doi:10.1016/j.ijpsycho.2012.07.002

47. Fairchild AJ, McDaniel HL. Best (but oft-forgotten) practices: mediation analysis. *Am J Clin Nutr*. 2017;105(6):1259-1271. doi:10.3945/ajcn.117.152546

48. Sarasso S, Boly M, Napolitani M, et al. Consciousness and Complexity during Unresponsiveness Induced by Propofol, Xenon, and Ketamine. *Curr Biol*. 2015;25(23):3099-3105. doi:10.1016/j.cub.2015.10.014

49. Murphy M, Bruno MA, Riedner BA, et al. Propofol anesthesia and sleep: a high-density EEG study. *Sleep*. 2011;34(3):283-291A. doi:10.1093/sleep/34.3.283

50. Brown Emery N., Lydic Ralph, Schiff Nicholas D. General Anesthesia, Sleep, and Coma. *N Engl J Med*. 2010;363(27):2638-2650. doi:10.1056/NEJMra0808281

51. Purdon PL, Pierce ET, Mukamel EA, et al. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *Proc Natl Acad Sci*. 2013;110(12):E1142-E1151. doi:10.1073/pnas.1221180110

52. Xu Y, Guo H, Zheng R, et al. Decreased intrinsic neural timescales in obsessive compulsive disorder and two distinct subtypes revealed by heterogeneity through discriminative analysis. *J Affect Disord*. 2023;340:667-674. doi:10.1016/j.jad.2023.07.112

53. Watanabe T, Rees G, Masuda N. Atypical intrinsic neural timescale in autism. *eLife*. 2019;8:e42256. doi:10.7554/eLife.42256

54. Northoff G, Sandsten KE, Nordgaard J, Kjaer TW, Parnas J. The Self and Its Prolonged Intrinsic Neural Timescale in Schizophrenia. *Schizophr Bull*. 2021;47(1):170-179. doi:10.1093/schbul/sbaa083

55. Uscătescu LC, Said-Yürekli S, Kronbichler L, et al. Reduced intrinsic neural timescales in schizophrenia along posterior parietal and occipital areas. *Npj Schizophr*. 2021;7(1):55. doi:10.1038/s41537-021-00184-x

56. Zhang A, Wengler K, Zhu X, et al. *Altered Hierarchical Gradients of Intrinsic Neural Timescales in Mild Cognitive Impairment and Alzheimer's Disease*. Neuroscience; 2023. doi:10.1101/2023.09.26.559549

57. Golesorkhi M, Gomez-Pilar J, Zilio F, et al. The brain and its time: intrinsic neural timescales are key for input processing. *Commun Biol*. 2021;4(1):1-16. doi:10.1038/s42003-021-02483-6

58. Bazanova OM, Vernon D. Interpreting EEG alpha activity. *Neurosci Biobehav Rev*. 2014;44:94-110. doi:10.1016/j.neubiorev.2013.05.007

59. Synek VM. The Low-Voltage Electroencephalogram. *Clin Electroencephalogr*. 1983;14(2):102-105. doi:10.1177/155005948301400211

60. Anokhin A, Steinlein O, Fischer C, et al. A genetic study of the human low-voltage electroencephalogram. *Hum Genet*. 1992;90(1-2):99-112. doi:10.1007/BF00210751

61. Young MJ, Edlow BL, Bodien YG. Covert consciousness. *NeuroRehabilitation*. 2024;54(1):23-42. doi:10.3233/NRE-230123

62. Schnakers C, Bauer C, Formisano R, et al. What names for covert awareness? A systematic review. *Front Hum Neurosci*. 2022;16:971315. doi:10.3389/fnhum.2022.971315

63. Schiff ND. Cognitive Motor Dissociation Following Severe Brain Injuries. *JAMA Neurol*. 2015;72(12):1413-1415. doi:10.1001/jamaneurol.2015.2899

64. Delorme A. EEG is better left alone. *Sci Rep*. 2023;13(1):2372. doi:10.1038/s41598-023-27528-0

65. Tröndle M, Popov T, Pedroni A, Pfeiffer C, Barańczuk-Turska Z, Langer N. Decomposing age effects in EEG alpha power. *Cortex*. 2023;161:116-144. doi:10.1016/j.cortex.2023.02.002

66. O'Gorman RL, Poil SS, Brandeis D, et al. Coupling Between Resting Cerebral Perfusion and EEG. *Brain Topogr*. 2013;26(3):442-457. doi:10.1007/s10548-012-0265-7

67. Kirschfeld K. The physical basis of alpha waves in the electroencephalogram and the origin of the "Berger effect." *Biol Cybern*. 2005;92(3):177-185. doi:10.1007/s00422-005-0547-1

68. Lewine JD, Plis S, Ulloa A, et al. Quantitative EEG Biomarkers for Mild Traumatic Brain Injury. *J Clin Neurophysiol*. 2019;36(4):298. doi:10.1097/WNP.0000000000000588

69. Bentes C, Peralta AR, Viana P, et al. Quantitative EEG and functional outcome following acute ischemic stroke. *Clin Neurophysiol*. 2018;129(8):1680-1687. doi:10.1016/j.clinph.2018.05.021

70. Maschke C, Belloli L, Manasova D, Sitt JD, Blain-Moraes S. The role of etiology in the identification of clinical markers of consciousness: comparing EEG alpha power, complexity, and spectral exponent. Published online March 22, 2024:2024.03.20.24304639. doi:10.1101/2024.03.20.24304639

71. Neveu A, Degos V, Barberousse A. Epistemological challenges for neural correlates of consciousness: A defense of medical research on consciousness. *Presse Médicale*. 2023;52(2):104183. doi:10.1016/j.lpm.2023.104183