OXFORD

Cerebral Cortex, 2023, 1–18
https://doi.org/10.1093/cercor/bhad031
Original Article

Beyond alpha power: EEG spatial and spectral gradients robustly stratify disorders of consciousness

Michele Angelo Colombo[1,†], Angela Comanducci[2,3,†], Silvia Casarotto[1,2], Chiara-Camilla Derchi[2], Jitka Annen[4], Alessandro Viganò[2], Alice Mazza[2], Pietro Davide Trimarchi[2], Melanie Boly[5], Matteo Fecchio[6], Olivier Bodart[4], Jorge Navarro[2], Steven Laureys[4], Olivia Gosseries[4], Marcello Massimini[1,2], Simone Sarasso[1], Mario Rosanova[1,*]

[1]Department of Biomedical and Clinical Sciences, University of Milan, Milan 20157, Italy,
[2]IRCCS, Fondazione Don Carlo Gnocchi Onlus, Milan 20148, Italy,
[3]Department of Engineering, Università Campus Bio-Medico di Roma, Rome 00128, Italy,
[4]Coma Science Group, GIGA-Consciousness, University of Liège and Centre du Cerveau2, University Hospital of Liège, Liège 4000, Belgium,
[5]Department of Neurology and Department of Psychiatry, University of Wisconsin, Madison, WI 53705-2281, USA,
[6]Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital, Boston, MA 02114, USA

*Corresponding author: Dipartimento di Scienze Biomediche e Cliniche, Università Degli Studi di Milano, 20157 Milan, Italy. Email: mario.rosanova@unimi.it

†Michele A. Colombo and Angela Comanducci have contributed equally to this work.

Neurophysiological markers can overcome the limitations of behavioural assessments of Disorders of Consciousness (DoC). EEG alpha power emerged as a promising marker for DoC, although long-standing literature reported alpha power being sustained during anesthetic-induced unconsciousness, and reduced during dreaming and hallucinations. We hypothesized that EEG power suppression caused by severe anoxia could explain this conflict. Accordingly, we split DoC patients ($n = 87$) in postanoxic and non-postanoxic cohorts. Alpha power was suppressed only in severe postanoxia but failed to discriminate un/consciousness in other aetiologies. Furthermore, it did not generalize to an independent reference dataset ($n = 65$) of neurotypical, neurological, and anesthesia conditions. We then investigated EEG spatio-spectral gradients, reflecting anteriorization and slowing, as alternative markers. In non-postanoxic DoC, these features, combined in a bivariate model, reliably stratified patients and indexed consciousness, even in unresponsive patients identified as conscious by an independent neural marker (the Perturbational Complexity Index). Crucially, this model optimally generalized to the reference dataset. Overall, alpha power does not index consciousness; rather, its suppression entails diffuse cortical damage, in postanoxic patients. As an alternative, EEG spatio-spectral gradients, reflecting distinct pathophysiological mechanisms, jointly provide a robust, parsimonious, and generalizable marker of consciousness, whose clinical application may guide rehabilitation efforts.

Key words: severe brain injury; anesthesia; spectral exponent; anterior–posterior gradient; TMS-EEG.

Introduction

The diagnosis of Disorders of Consciousness (DoC) following severe brain-injury impacts prognosis, as well as treatment, rehabilitation, and end-of-life decisions (Giacino et al. 2014; Giacino et al. 2018a). Currently, the differential diagnosis of DoC between the Minimally Conscious State (MCS) and the Unresponsive Wakefulness Syndrome (UWS, also known as Vegetative State, VS) relies on repeated behavioural assessments through the Coma Recovery Scale-Revised (CRS-R) (Giacino et al. 2004, 2009), which can be unreliable due to patient's sensorimotor and executive deficits (Giacino et al. 2009).

To assist the diagnostic process of DoC, the visual inspection of spontaneous EEG recordings is strongly recommended by most recent guidelines from the European Academy of Neurology (Kondziella et al. 2020). Quantitative-EEG (qEEG) analysis should follow thereafter, according to a recent expert opinion of leading clinicians and researchers on the topic (Comanducci et al. 2020). Multiple qEEG features (Bai et al. 2017; Engemann et al. 2018; Corchs et al. 2019; Wutzl et al. 2021) can be combined by machine-learning methods to improve performance, although high model complexity comes at the expense of generalizability, interpretability, and pathophysiological understanding (James et al. 2013; Noirhomme et al. 2017).

Alpha power demonstrated high diagnostic power in previous studies of DoC (Lehembre et al. 2012; Chennu et al. 2014; Sitt et al. 2014; Rossi Sebastiano et al. 2015; Naro et al. 2016; Piarulli et al. 2016; Lutkenhoff et al. 2022). Accordingly, in the largest study of qEEG in DoC (Engemann et al. 2018), absolute alpha power emerged among more than hundred spectral, complexity, and connectivity features as the most prominent feature to distinguish MCS from UWS patients and strongly drove the ensemble model's decisions. These findings led to the notion that alpha rhythm represents the "rhythm of a conscious brain" (Sokoliuk and Cruse 2018).

In stark contrast, several lines of evidence outside the literature of DoC suggest that alpha power is not a general marker of consciousness. On the one hand, alpha power can be enhanced/preserved during unconsciousness induced by general anesthesia,

Received: October 26, 2022. **Revised:** January 17, 2023. **Accepted:** January 18, 2023

for instance with propofol or ether-derived compounds (Ching et al. 2010; Vijayan et al. 2013; Purdon et al. 2015; Scheinin et al. 2018). On the other hand, alpha power can be reduced despite consciousness being present, during disconnected consciousness, such as REM dreams (Benca et al. 1999; Esposito et al. 2004; Baird et al. 2018) and ketamine dreams (Akeju et al. 2016; Vlisides et al. 2017), or during psychedelic states induced by serotonergic agents (Muthukumaraswamy et al. 2013; Schartner et al. 2017; Muthukumaraswamy and Liley 2018; Timmermann et al. 2019). Altogether, these findings question the role of alpha power as a marker of consciousness following severe brain injury.

The discrepancy between the two literatures may originate from the distinct neurophysiology of severe postanoxic brain-injury, which may have conflated the diagnostic relevance of alpha power in the context of DoC. Anoxia is a major aetiology among UWS patients (van Erp et al. 2015) and typically causes chronic unresponsiveness (Bernat 2006; Katz et al. 2009; Estraneo et al. 2013; Howell et al. 2013). Prolonged anoxia typically leads to severe diffuse cortical damage, as reflected by the low-voltage EEG pattern (Cloostermans et al. 2012; Bauer et al. 2013; Rossi Sebastiano et al. 2015; Estraneo et al. 2016; Hofmeijer and van Putten 2016; Rossetti et al. 2016), an overall suppression of EEG rhythms also known as hypo-voltage—associated to poor outcome in comatose (Hofmeijer et al. 2015) and DoC patients (Bagnato et al. 2015)—which may be most evident in the alpha-band. Indeed, patients with postanoxic DoC did not display any alpha-beta activity, according to the "ABCD" visual scoring system (Forgacs et al. 2017), and postanoxic unresponsive patients had the lowest occurrence of theta-alpha spectral patterns, according to automated classification (Fingelkurts et al. 2013).

Here, we first explicitly investigate whether alpha power may particularly index the overall suppression of cortical activity (low-voltage) typical of severe postanoxic damage, rather than the absence of consciousness per se. Second, we propose prominent spatial and spectral gradients of the spontaneous-EEG as reliable alternatives for the diagnosis of DoC. Finally, to overcome the limitations of behavioural assessments (Sanders et al. 2012) and to strengthen the validity of our findings, we assessed the capacity for consciousness beyond sheer behavioural responsiveness and generalized the predictions obtained in DoC to known conditions of a reference dataset.

To the first aim, we separately considered anoxic patients from DoC of other aetiologies and investigated the specific role of alpha power in indexing severe postanoxic damage.

To the second aim, we distilled physiological, neurological, and pharmacological literature of loss of consciousness and assessed changes in EEG spatial and spectral gradients as robust and general markers of consciousness (see Fig. 1 for a schematic depiction of the selected EEG features). Specifically, we considered the EEG anteriorization, by assessing the alpha postero-anterior organization (De Gennaro et al. 2001; Ogilvie 2001; Ching et al. 2010; Vijayan et al. 2013; Purdon et al. 2015; Scheinin et al. 2018), and the broad-band slowing, by assessing the Spectral Exponent (He et al. 2010; Miskovic et al. 2018; Colombo et al. 2019; Zilio et al. 2021; Maschke et al. 2022).

To test the generalizability of the observations on DoC patients, we included in a reference dataset communicating patients with widely different brain-injuries, as well as neurotypical subjects during wakefulness and anesthesia—leading to either unconsciousness or disconnected consciousness. Importantly, in doing all this, we established the proper conditions to overcome the limitations of behavioural assessments. Specifically, we assessed the reliability of the above-mentioned spontaneous-EEG markers against a novel scheme that explicitly attributes the capacity for consciousness during unresponsiveness, by means of an independent and highly sensitive neural index based on direct cortical perturbations, proposed by Casali and colleagues (Casali et al. 2013) and validated in DoC patients by Casarotto and colleagues (Casarotto et al. 2016).

Overall, we seek to rectify a common misconception about the value of alpha power in the classification of DoC. Moving beyond alpha power, we propose a parsimonious and interpretable approach based on the combination of two features—the EEG spatial and spectral gradients—which may provide a generalizable index of the capacity for consciousness following severe brain-injury.

Materials and methods

DoC population: DoC-Anoxia and DoC-Not-Anoxia dataset

We retrospectively recruited 87 severely brain-injured patients with DoC—72/87 previously included in Casarotto et al. (Casarotto et al. 2016)—from four different centers, whose local ethical committees approved the experimental protocols (Supplementary Materials S2.1 and S2.2). Patients were included at least 1 week from the injury date and had acute ($n = 9$), prolonged ($n = 23$), and chronic ($n = 55$) DoC—according to the recently proposed temporal definitions (Giacino et al. 2018a). Patients were diagnosed as either UWS, MCS−, MCS+ according to the best CRS-R assessment, applied at least 3 times within 1 week. We included DoC patients of vascular ($n = 37$), traumatic ($n = 22$), and anoxic ($n = 28$) aetiologies. Given the unique natural history of postanoxic DoC (Rossetti et al. 2016; Giacino et al. 2018a), and its distinct neurophysiological signatures (Cloostermans et al. 2012; Bauer et al. 2013; Rossi Sebastiano et al. 2015; Casarotto et al. 2016; Estraneo et al. 2016; Hofmeijer and van Putten 2016; Rossetti et al. 2016), we considered postanoxic patients with DoC separately. In our database, the majority of postanoxic patients were clinically in a UWS (20/28). We thus split our DoC population into a "DoC-Anoxia" dataset (20 UWS, 5 MCS−, 3 MCS+ patients) and a "DoC-Not-Anoxia" dataset (27 UWS, 17 MCS−, 15 MCS+ patients). Traumatic and vascular patients with DoC showed highly consistent neurophysiological results when considered separately (Supplementary Fig. 4) or jointly (main text). The two DoC datasets did not differ for time since injury, or age ($P = 0.17$, $P = 0.37$, respectively; details in Supplementary Table 1). All prolonged and chronic patients with DoC were free from sedative drugs; acute patients were so from at least 7 days.

Reference dataset

The Reference dataset consisted of conditions where individuals could confirm the presence/absence of consciousness, by functional communication or by immediate/delayed reports. The Reference dataset included: (i) neurotypical individuals during wakefulness (Wakefulness with Eyes Closed, Wakefulness with Eyes Open) and different anesthetic conditions (Xenon, Propofol, Ketamine), reported in Colombo et al. (2019) and in Sarasso et al. (2015) ($n = 30$); (ii) patients with stroke (Cortical Stroke, SubCortical Stroke) ($n = 22$), 20 of which reported in Sarasso et al. (2020); (iii) Emergence from a previous MCS (EMCS) and Locked-In Syndrome (LIS) patients ($n = 13$), 11 of which previously reported in Casarotto et al. (2016). Further details are reported in Fig. 2, in Supplementary Material S2.3, and Supplementary Table 1.

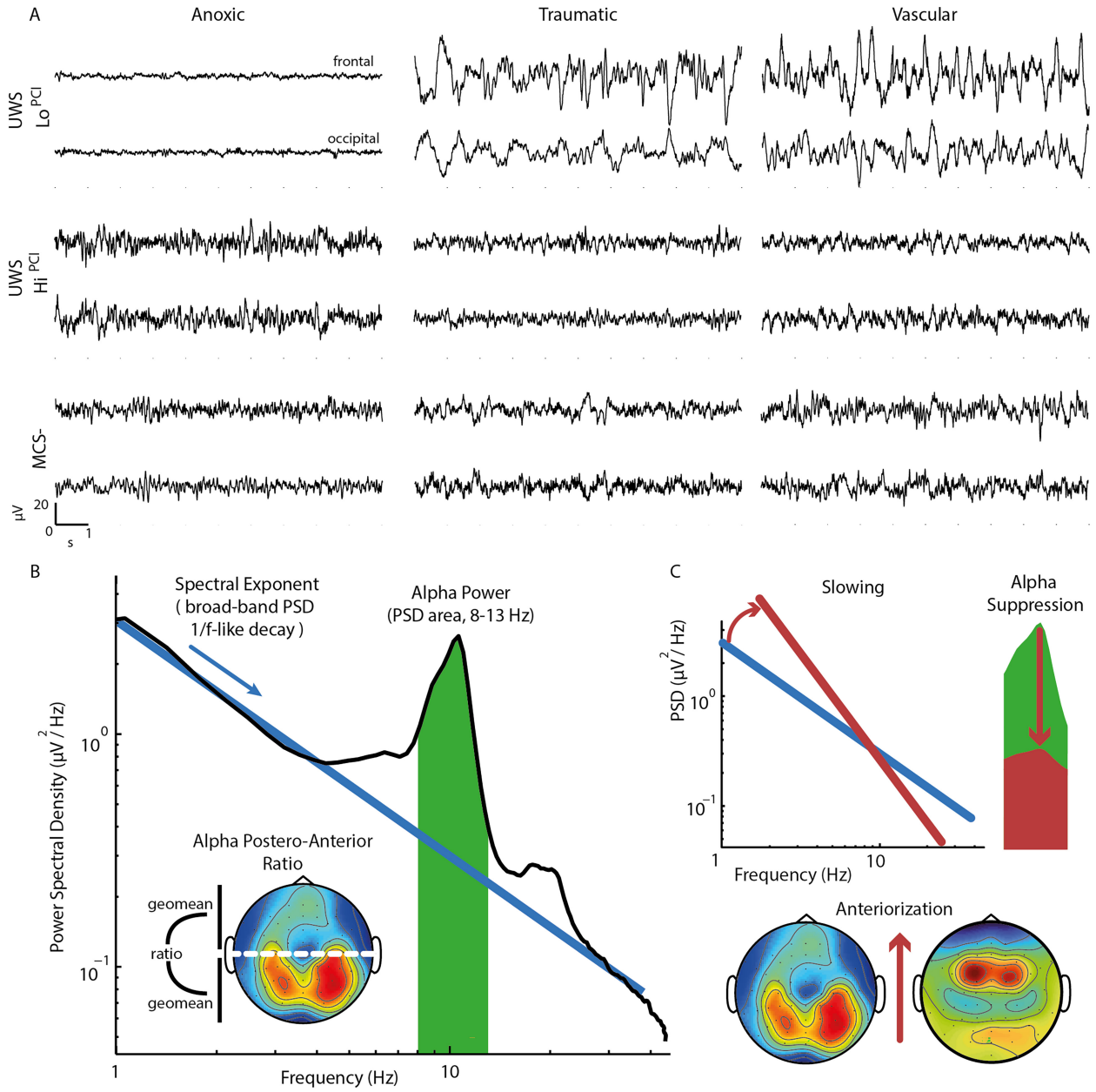

Fig. 1. Examples of spontaneous EEG traces of DoC patients across aetiologies; quantification of the EEG spectral features and expected changes upon loss of consciousness. A) Illustrative examples of spontaneous EEG traces (10 s) from frontal and occipital electrodes (upper and lower traces, respectively) of representative DoC patients. Each column corresponds to a different aetiology: anoxic, traumatic, and vascular. Each row corresponds to a different patient group: UWS with Lo^{PCI} (Casali et al. 2013; Casarotto et al. 2016) (consistent with unresponsiveness and unconsciousness, see Methods section: 'Prior neural evidence: Perturbational Complexity Index'), UWS with Hi^{PCI} (c/w unresponsiveness and capacity for consciousness), and MCS− (c/w responsiveness and capacity for consciousness). The anoxic UWS patient with Lo^{PCI} shows a low-voltage EEG; conversely, traumatic and vascular UWS patients with Lo^{PCI} show a higher degree of EEG slowing and anteriorization, with respect to UWS patients with Hi^{PCI} and MCS− patients alike. B) Alpha Power indexes the ($\log_{10}$ of the) PSD area between 8 and 13 Hz; thereby quantifying overall EEG alpha activity—the main rhythm of neurotypical wakefulness. Alpha Postero-Anterior Ratio indexes the ratio of (the regional geometric mean of) alpha power between posterior and anterior regions, thereby quantifying the degree of EEG anteriorization. The Spectral Exponent indexes the steepness of the PSD decay over frequencies (1/*f*-like), thereby quantifying overall broad-band EEG slowing. C) Lower alpha power appears physiologically during sleep onset, pathologically after cortical/thalamocortical structural damage; yet, pharmacological agents can yield high alpha power while suppressing consciousness, or viceversa, can reduce alpha power while retaining consciousness. Lower Alpha Postero-Anterior Ratio values index the disruption of the neurotypical posterior-to-anterior gradient, up to the reversal of the gradient (values $<< 1$). Anteriorization is typically observed in physiological, pharmacological, and neurological loss of consciousness. More negative Spectral Exponent values index a steeper decay, hence an overall slower EEG activity. Slowing is typically observed in physiological, pharmacological, and neurological loss of consciousness.

Prior *behavioural* classification and stratification

In the DoC population, the diagnosis based on CRS-R led to a natural dichotomic *behavioural* classification: behaviourally unresponsive (B−: UWS) and behaviourally responsive patients (B+: MCS−, MCS+). The Reference dataset consisted of behaviourally unresponsive (B-: 5 Xenon, 5 Propofol, and 5 Ketamine) and behaviourally responsive subjects (B+: 9 EMCS; 4 LIS; 10 Cortical Stroke, 12 SubCortical Stroke, 10 Wakefulness with Eyes Closed, 5 Wakefulness with Eyes Open).

Furthermore, we stratified patients' groups based on their responsiveness on 4 levels (A, B, C, D), ranging from unresponsiveness, through intentional acts and command following, to the

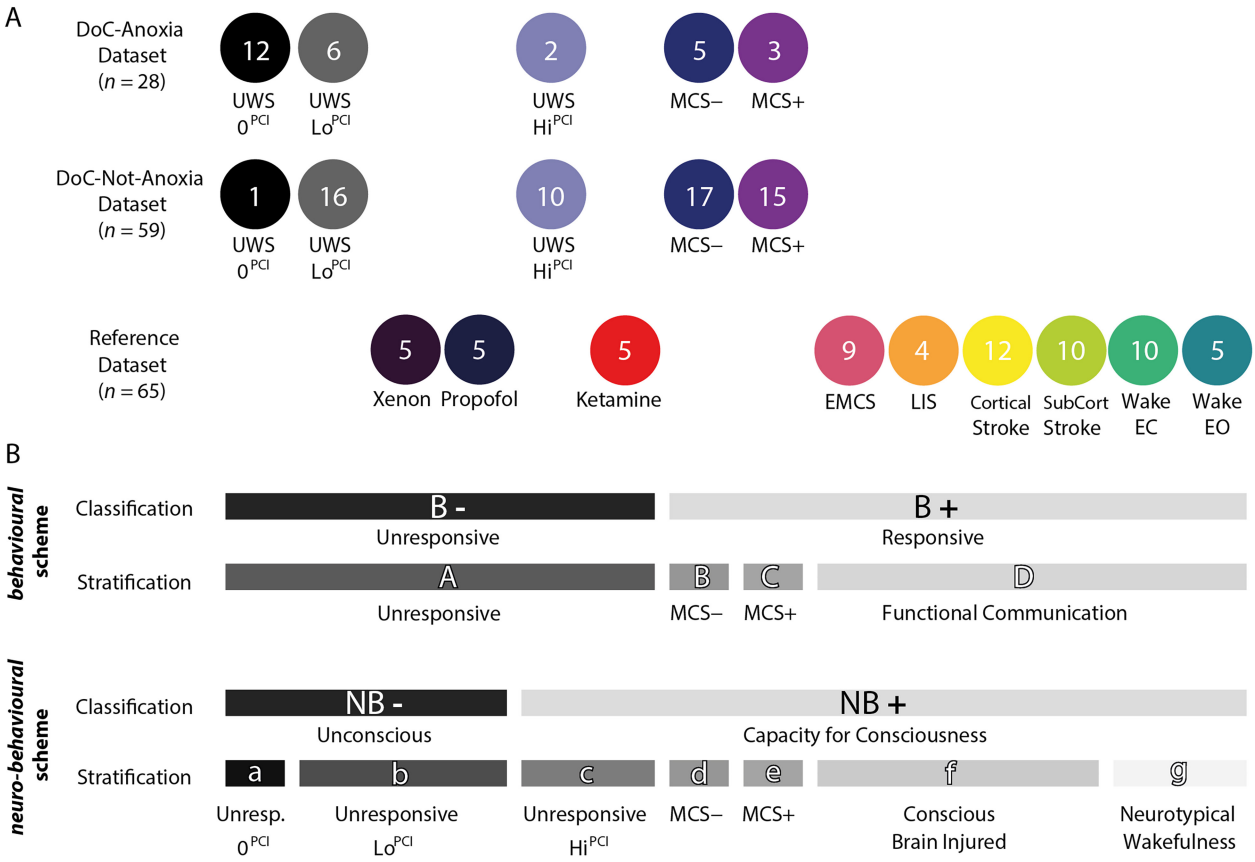

Fig. 2. The *neuro-behavioural* scheme provides a classification and stratification of subjects across the three datasets, by integrating neural evidence into the *behavioural* scheme. A) We analyzed three datasets: a DoC-Anoxia dataset, composed of postanoxic DoC patients (mostly UWS, following their natural history); a DoC-Not-Anoxia dataset, composed of DoC patients with vascular or traumatic aetiologies; and a Reference dataset, composed of conscious patients with brain injury, neurotypical individuals during wakefulness and in three unresponsive conditions of anesthesia: Xenon, Propofol (yielding no conscious reports and Lo^{PCI}), and Ketamine (yielding delayed conscious reports and Hi^{PCI}). B) According to the *behavioural* scheme, the classification reflected the presence/absence of behavioural responsiveness (assessed by the CRS-R in DoC and severely brain-injured patients, by the Ramsay-scale during anesthesia, or by functional communication otherwise); groups of patients were stratified according to 4 levels (A–D). According to the *neuro-behavioural* scheme, the classification reflected the presence/absence of the capacity for consciousness, estimated from the best outcome from behavioural and neural evidence (PCI-max values grouped into zero or low values vs high values). Furthermore, groups of patients were stratified according to 7 levels (a–g), thus refining the *behavioural* stratification on the lower end according to PCI-max (reflecting the complexity of EEG patterns evoked by direct cortical perturbations) and on the upper end according to the presence/absence of a brain injury. Abbreviations within the figure: SubCort Stroke= SubCortical Stroke; Wake EC = Wakefulness with Eyes Closed; Wake EO = Wakefulness with Eyes Open

recovery of functional communication (Fig. 2). Lower stratification ranks corresponded to a higher degree of *behavioural* impairment (hereby defined). In the DoC datasets, UWS, MCS−, and MCS+ were, respectively, ranked as A,B, and C; in the Reference dataset, Xenon together with Propofol and Ketamine was ranked as A, then Stroke (Cortical or SubCortical) together with LIS, EMCS, and Wakefulness (with Eyes Closed or Open) as D.

Prior neural evidence: Perturbational Complexity Index

We gathered prior neural evidence that allowed us to define signs of retained capacity for consciousness irrespective of behavioural responsiveness. Specifically, we estimated the complexity of the EEG responses evoked by Transcranial Magnetic Stimulation (TMS), by means of the Perturbational Complexity Index (PCI) (Casali et al. 2013). Patients included in the current study largely overlap with those previously reported in Casarotto et al. (2016) ($n = 104$ across datasets), where the procedure is described extensively (see also Supplementary Material). Briefly, the highest individual PCI value across stimulation sites (PCI-max) was retained and identified three categories of TMS-evoked EEG responses:

-**0^{PCI}:** no significant response could be evoked (PCI-max = 0), the most severe pattern, indexing absent cortical reactivity and thereby unconsciousness;

-**Lo^{PCI}**: low complexity (PCI-max ≤ 0.31), indexing unconsciousness;

-**Hi^{PCI}**: high complexity (PCI-max > 0.31), indexing preserved capacity for consciousness.

Prior *neuro-behavioural* classification and stratification

The *neuro-behavioural* classification combined the best result available from previously gathered behavioural and neural evaluations (PCI-max), to attribute the presence/absence of capacity for consciousness (Fig. 2). As reported in Casarotto et al. (2016), while most UWS patients had 0^{PCI} or Lo^{PCI} values (UWS_0^{PCI}, UWS_Lo^{PCI}), a minority had Hi^{PCI} values (UWS_Hi^{PCI}); conversely nearly all MCS and all conscious brain-injured patients had Hi^{PCI} values. As reported in Colombo et al. (2019)), all individuals under Propofol or Xenon anesthesia had Lo^{PCI} values and reported no conscious experience upon awakening; conversely, all individuals under Ketamine anesthesia had Hi^{PCI} values and retrospectively reported vivid dreams upon awakening,

thus constituting a model of unresponsive consciousness. The *neuro-behavioural* classification defined in the two DoC datasets an unconscious class (NB−: UWS_0^{PCI}, UWS_Lo^{PCI}) and a conscious class (NB+: UWS_Hi^{PCI}, MCS−, MCS+); similarly, it defined in the Reference dataset an unconscious class (NB−: Xenon, Propofol) and a conscious class (NB+: Ketamine, EMCS, Cortical Stroke, SubCortical Stroke, LIS, Wakefulness with Eyes Closed, Wakefulness with Eyes Open). We leveraged on PCI-max to refine the lower end of the *behavioural* stratification in all datasets; furthermore, in the Reference dataset, we considered the presence/absence of a brain injury to refine the upper end. Lower stratification ranks corresponded to a higher degree of *neuro-behavioural* impairment (hereby specified): UWS_0^{PCI}, UWS_Lo^{PCI}, UWS_Hi^{PCI}, MCS−, MCS+ (respectively, ranked as a, b, c, d, e), in both DoC datasets; in the Reference dataset, Xenon together with Propofol (ranked as b), then Ketamine (c), then Stroke (Cortical or SubCortical) together with LIS and EMCS (f), then Wakefulness (with Eyes Closed or Open) (g).

Spontaneous EEG acquisition

During recordings, patients and healthy participants were seated in an upright or reclined position, in a quiet room. Short spontaneous EEG recordings (median = 5.13 min, interquartile range = 4.03–6.59 min) were acquired contextually to TMS-EEG in the same date ($n = 135$), or alternatively in a proximal session, occurring within one day ($n = 7$), or at most within two weeks ($n = 10$, median 6 days, all chronic patients). In these instances, the CRS-R *behavioural* diagnosis remained constant.

Trained personnel continuously monitored for any signs of sleepiness and, if needed, the CRS-R vigilance protocol was administered to ensure patients' vigilance (Giacino et al. 2004). This procedure avoided sleep intrusions and minimized the influence of arousal drops on the variables of interest.

EEG (Ag-Cl electrodes) was recorded with TMS-compatible EEG amplifiers (Nexstim Ltd, 60 channels, $n = 140$; Brain Products GmbH, 64-channels, $n = 12$). The two systems had very similar electrode locations (Supplementary Fig. 1) and their acquisition reference was ad-hoc placed on the forehead (near Fpz). Input-impedance was kept below 20 kOhms. Example EEG traces are shown in Fig. 1.

Within subject analysis of spontaneous EEG

Filtering, artifact rejection, and re-referencing

EEG was band-pass filtered (3rd-order Butterworth, 0.5–60 Hz cutoffs, filtfilt Matlab function) notch-filtered (50-Hz harmonics up to 250 Hz) and downsampled from the original sampling rate (Brain Products: from 5,000 to 1,000 Hz; Nexstim: from 1,450 to 725 Hz). A trained neurophysiologist manually rejected artifactual periods (retained minutes, percentage of time: median = 4.79 min, 98.74%, interquartile range = 3.58–6.12 min, 91.06–99.27%) and electrodes (rejected electrodes: median = 2, interquartile range: 1–4) (details in Supplementary Material). Artifactual electrodes were interpolated using spherical splines. Electrodes were then re-referenced to the common average.

Rejection of artifactual components through independent component analysis

Independent Component Analysis (ICA) decomposition allowed to visually identify and reject components from ocular, muscular, and cardiac origin (Supplementary Material S2.4). Overall, we retained a median of 33 components (interquartile range = 25–41.5). Clean EEG signals were then back-projected to the scalp.

EEG spectral features

We estimated the Power Spectral Density (PSD) of each electrode with Welch's method (3 s Hanning periodograms; 50% overlap). From the PSD, we operationalized three features of interest (Fig. 1, see introduction and Supplementary Material S1).

Alpha Power. To quantify the amount of alpha activity, we estimated the magnitude of absolute Alpha Power—$\log_{10}$ of the area under the PSD curve in the 8–13 Hz band, $\log_{10}(\mu V^2/Hz)$—then averaged across channels.

Alpha Postero-Anterior Ratio. We operationalized the EEG spatial gradient as the Alpha Postero-Anterior Ratio, to observe the anteriorization of EEG activity typically accompanying loss of consciousness, most commonly observed in the alpha band (Purdon et al. 2015). We estimated first the geometric mean of alpha power of posterior sites and that of anterior sites (according to the line connecting the ears and Cz, Supplementary Fig. 1), then the postero-anterior ratio. Values below 1 indexed that anterior alpha activity dominated over posterior activity.

Spectral Exponent. We operationalized the EEG spectral gradient as the Spectral Exponent, to observe the extent of broad-band EEG slowing. We estimated the $1/f$-like decay of the PSD background (i.e. disregarding oscillatory peaks) by means of the Spectral Exponent of the 1–40 Hz range, averaged across channels. More negative Spectral Exponent values index steeper spectral decay, hence a larger amplitude ratio of slow- over fast-frequencies, reflecting the slowing of broad-band arrhythmic or quasi-rhythmic activity (Palva and Palva 2018).

The procedure is fully detailed in Colombo et al. (2019), and the Matlab code is available online (https://github.com/milecombo/spectralExponent/). Figure 3 displays the PSD (averaged by geometric mean across electrodes and then groups) and the PSD arrhythmic $1/f$-like background.

Between subjects analysis: EEG-based classification and stratification

We assessed the agreement of the spontaneous EEG predictors (univariate features or multivariate statistical predictions) with the prior classification of the presence/absence of capacity for consciousness (classification) as well as with the prior stratification of the patients' groups (stratification). All analyses were performed according to the *neuro-behavioural* scheme (Figs. 4–6; see Supplementary Fig. 5 for the *behavioural* scheme). For classification analysis, the overall performance of spontaneous EEG predictors was evaluated nonparametrically, by means of the area under the Receiver-Operating Characteristic curve (*AROC*), and parametrically, by means of an unpaired T-test across groups (*T*-values). For stratification analysis, we assessed the rank correlation (Spearman's *Rho*) between the EEG predictors and the prior stratification of patient's groups (Fig. 2, only the ranks' relative order in each dataset was relevant). We controlled for the family-wise error rate of each test using the Bonferroni–Holm correction, according to the number of predictors (univariate or multivariate) assessed in each dataset (see test statistics in Table 1, and their relative *P*-values—raw and corrected—in Supplementary Table 2).

Behavioural outcome assessment and influence of time from injury

The main aim of the study was to assess EEG features diagnostic performance; thus, included DoC patients were mostly in the prolonged/chronic phase (51/59 not-anoxic patients and 27/28 of anoxic patients), where diagnosis is relatively stable over time. Thus, we verified the outcome after one year, in a

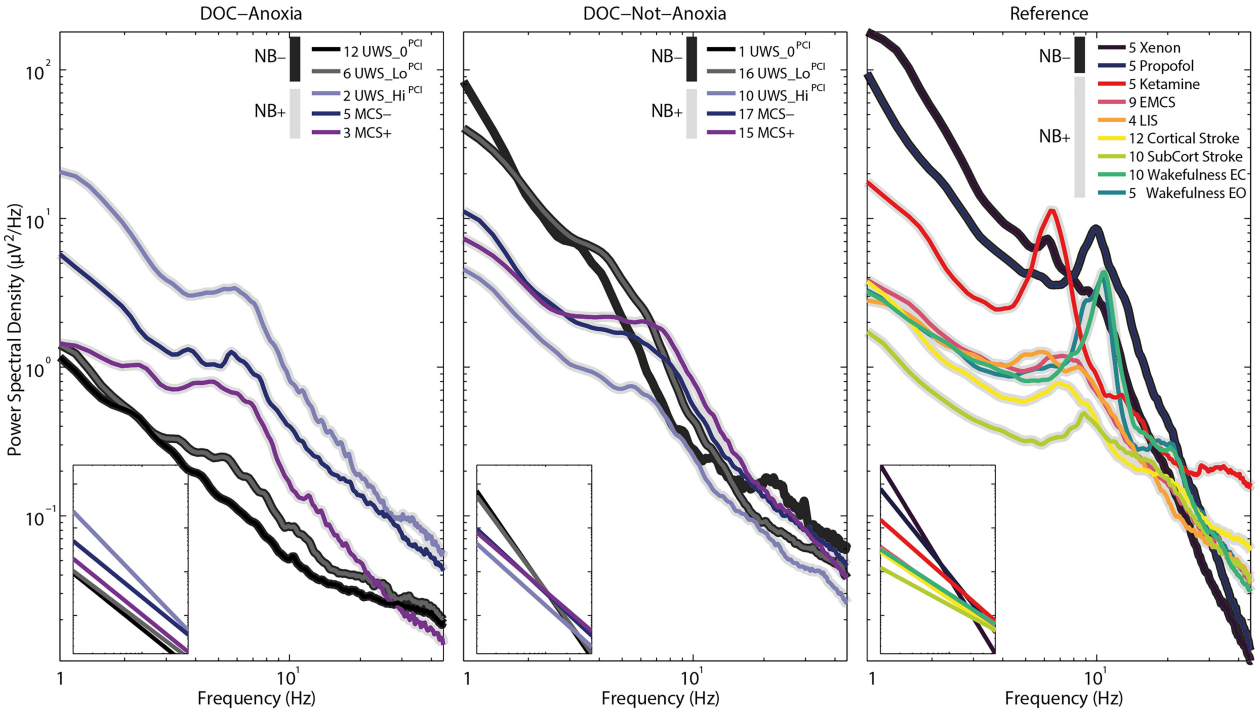

Fig. 3. Unconsciousness entails a broad-band power suppression in postanoxic patients, whereas it implies a clock-wise rotation of the PSD in not-anoxic patients and in reference conditions. PSD is shown for each group, in each of the three datasets, from left to right: DoC-Anoxia, DoC-Not-Anoxia, and Reference dataset. Geometric mean is used to average across electrodes (first) and individuals (subsequently), accounting for the exponential PSD distribution. Inlet graphs show the 1/*f*-like fit of the PSD over the 1–40 Hz, yielding a straight line in log–log coordinates. Unconscious individuals (UWS_0^{PCI} and UWS_Lo^{PCI}) show suppressed power in the DoC-Anoxia dataset, maximally in UWS_0^{PCI}. In the DoC-Not-Anoxia and in the Reference dataset, the PSD rotates clockwise (implying a steeper PSD decay and thus broad-band slowing) from conscious to unconscious conditions, as highlighted by the inlet graphs. Abbreviations within the figure: Wakefulness EC = Wakefulness with Eyes Closed; Wakefulness EO = Wakefulness with Eyes Open; Previously it mentioned: Wake EC = Wakefulness with Eyes Closed; Wake EO = Wakefulness with Eyes Open. A dark outline was used for the unconscious groups (NB–), a clear outline for the conscious group (NB+).

Table 1. Classification and stratification performances, for the *behavioral* and the *neuro-behavioural* scheme, of the predictors: three spontaneous-EEG features and the bivariate regression model.

Test	Predictor	DoC-Anoxia		DoC-Not-Anoxia		Reference	
		behavioural	*neuro-behavioural*	*behavioural*	*neuro-behavioural*	*behavioural*	*neuro-behavioural*
T-test Classification	Alpha Power	**−2,47**	**−4,15**	**−3,31**	−0,76	**3,27**	**3,94**
	Alpha PostAntRatio	−1,62	−1,23	**−3,53**	**−4,39**	**−5,75**	**−7,09**
	Spectral Exponent	0	0,79	**−4**	**−6,91**	**−9,41**	**−12,09**
	PLS1 DoC-Not-Anoxia	−0,93	−0,26	**−4,66**	**−7,47**	**−8,9**	**−11,78**
AROC Classification	Alpha Power	0,788	**0,889**	**0,738**	0,591	**0,785**	**0,864**
	Alpha PostAntRatio	0,706	0,661	**0,742**	**0,84**	**0,844**	**0,936**
	Spectral Exponent	0,475	0,633	**0,795**	**0,941**	**0,935**	**1**
	PLS1 DoC-Not-Anoxia	0,613	0,528	**0,817**	**0,964**	**0,943**	**1**
***Rho* Stratification**	Alpha Power	0,423	**0,571**	**0,451**	**0,387**	**−0,416**	−0,021
	Alpha PostAntRatio	0,325	0,265	**0,422**	**0,496**	**0,502**	**0,677**
	Spectral Exponent	−0,028	−0,094	**0,502**	**0,612**	**0,634**	**0,518**
	PLS1 DoC-Not-Anoxia	0,184	0,129	**0,547**	**0,656**	**0,646**	**0,704**

Tests were performed separately according to the *behavioural* scheme and to the *neuro-behavioural* scheme. See Fig. 2 for the prior classification and stratification schemes across groups. Classification performance is quantified by the *T* and *AROC* values, Stratification by the *Rho* values. The degrees of freedom for the *T*-test and the Spearman correlation were 26 in the Doc-Anoxia dataset, 57 in the Doc-Not-Anoxia dataset, and 63 in the Reference dataset. Bold highlights statistically significant values, after family-wise Bonferroni–Holm correction (4 tests in each family: 3 features and 1 model, $P < 0.05$); see Supplementary Table 2 for raw and corrected *P*-values. PLS1 DoC-Not-Anoxia = Partial Least Square Bivariate regression model with 1 component trained on the DoC-Not-Anoxia dataset. Alpha PostAntRatio = Alpha Postero-Anterior Ratio.

subset of DoC patients where we could retrieve the information (42/59 not-anoxic patients and 24/28 anoxic). Patient's diagnosis remained typically unchanged, particularly so for anoxic patients (Supplementary Material). We also conducted supplementary analysis to assess the influence of time from injury on EEG features. We observed that time from injury normalized EEG features, yet no effects or marginally significant effects were observed once controlling for the effects related to the capacity for consciousness; conversely, controlling for the influence of time from injury on EEG features did not alter the main effects related to the capacity for consciousness (Supplementary Material).

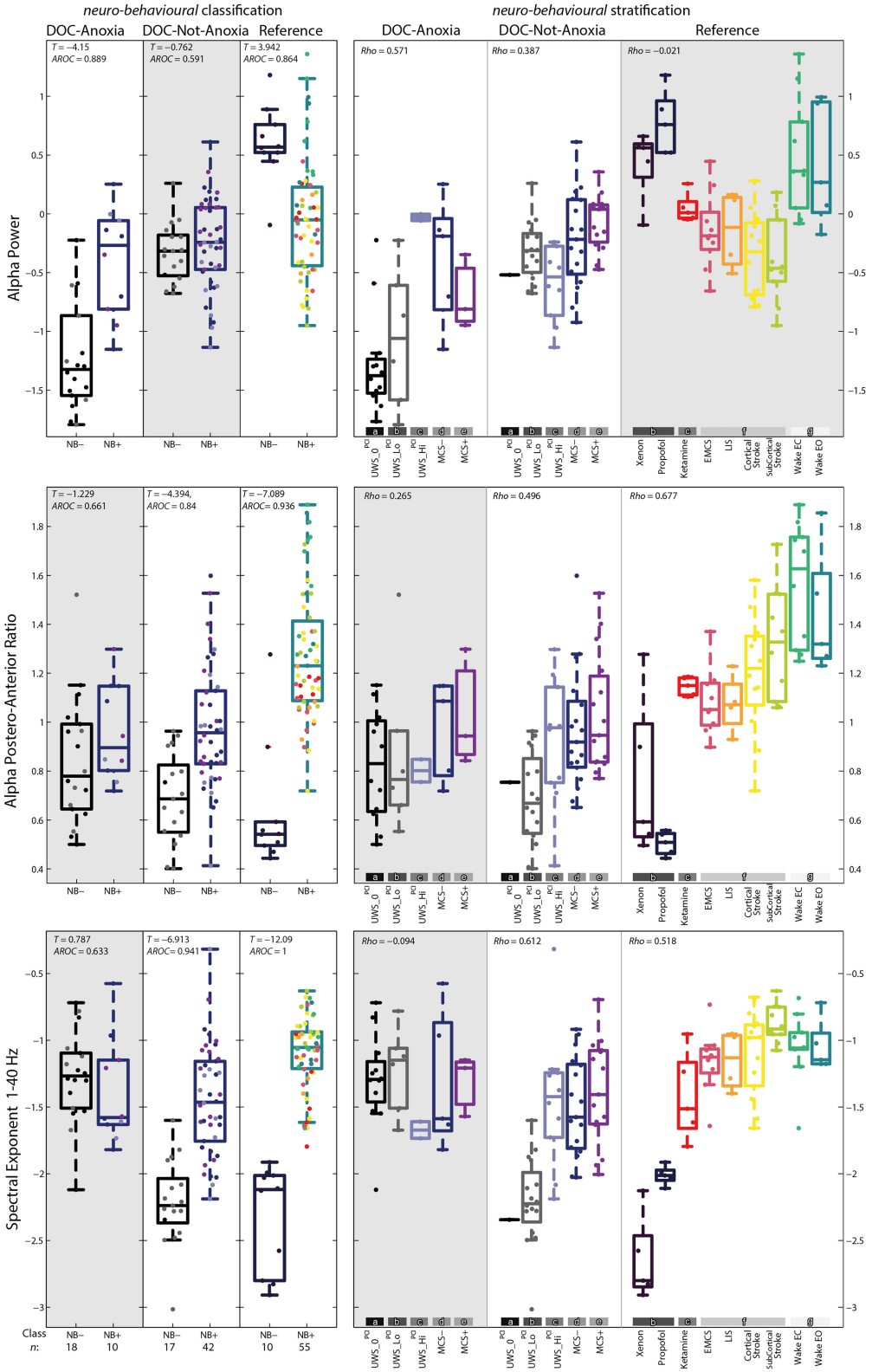

Fig. 4. Alpha Power was suppressed only in severe postanoxic DoC patients—maximally in UWS with 0^{PCI}; whereas lower Alpha Postero-Anterior Ratio and Spectral Exponent—respectively indexing anteriorization and slowing—predicted unconsciousness in both the DoC-Not-Anoxia and in the Reference dataset. Features from the spontaneous EEG yielded univariate quantitative values, which were compared in each dataset to the *neuro-behavioural* scheme (Fig. 2). The performance of the classification of the capacity for consciousness (NB− vs NB+, left-side) is quantified by *T*-values and by the area under the receiver operator characteristic (*ROC*) curve (*AROC*). The performance of the stratification (ranks, right-side) is quantified by the Spearman correlation between the features' values and the prior stratification of groups (ranked according to the letter's order), resulting in *Rho* values. Light gray background is shown where no significant association is observed. Classification performances are similar for traumatic and vascular DoC patients (composing the DoC-Not-Anoxia dataset), as shown in Supplementary Fig. 4. Abbreviations within the figure: Wake EO = Wakefulness with Eyes Open; Wake EC = Wakefulness with Eyes Closed.

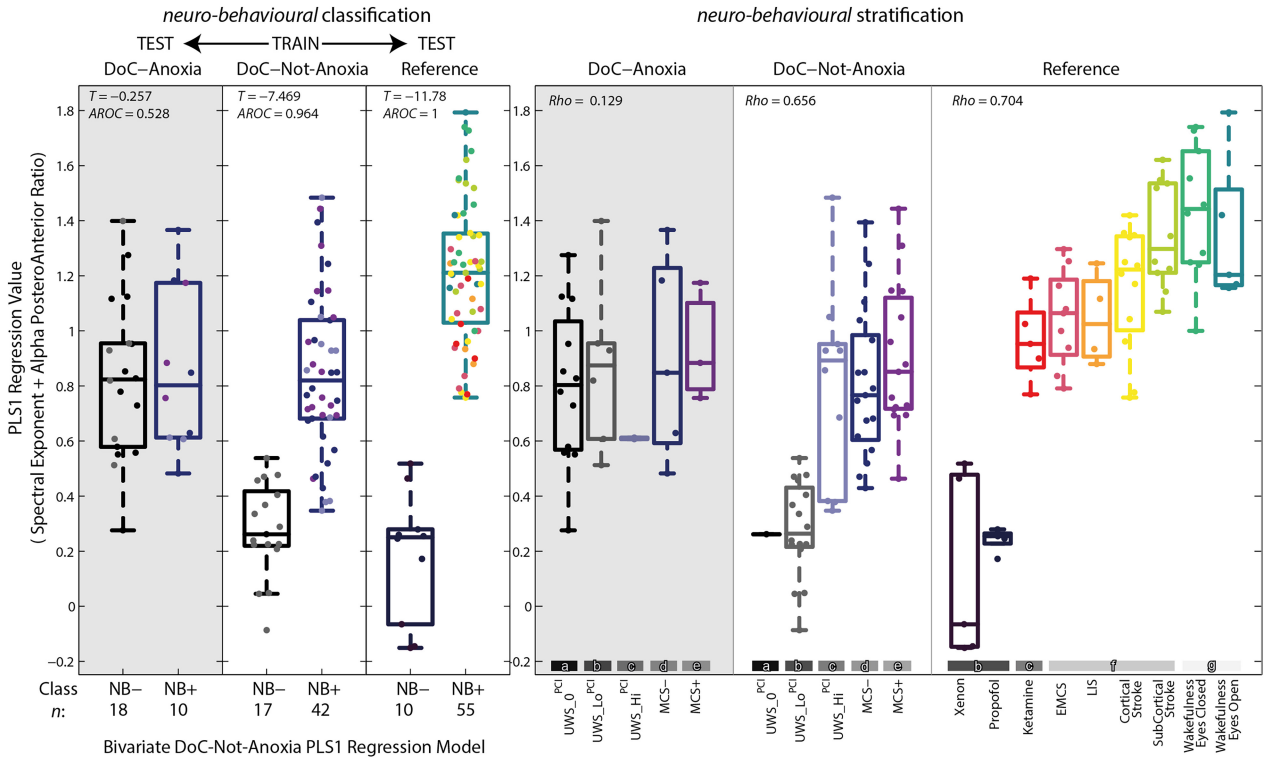

Fig. 5. The bivariate model, combining the Spectral Exponent and the Alpha Postero-Anterior Ratio, robustly performed on the training DoC-Not-Anoxia dataset, and optimally generalized to the Reference dataset, but not to the DoC-Anoxia dataset. The linear PLS regression model combined the Spectral Exponent and the Alpha Postero-Anterior Ratio into one component (PLS1). Such bivariate regression model was trained to predict the capacity for consciousness in the DoC-Anoxia dataset (classification: NB− vs NB+, left-side); the resulting values defined an empirical stratification of groups (right-side), which were compared with the prior *neuro-behavioural* stratification of groups (Fig. 2), by means of Spearman's rank-correlation. Classification performance (*T*-values, *AROC*) and stratification performance (*Rho*) are reported as in Fig. 4. Light gray background is shown where no significant association is observed. The bivariate regression model displayed high performance in the DoC-Anoxia dataset and maximal generalization performance in the Reference dataset, but it did not generalize to the DoC-Anoxia dataset.

Multivariate analysis: partial least square model

Following univariate analysis, the three spectral features were selected according to their univariate *neuro-behavioural* classification performance. The selected features were z-scored and jointly combined into a multivariate regression model. Specifically, a partial least square model (PLS, *plsregress* function in Matlab) aggregated the selected features into a single component (PLS1), to statistically predict the presence/absence of the capacity for consciousness (numerically encoded as 1/0). The predicted continuous regression values were subsequently also used for stratification analysis.

PLS DoC models: trained on DoC datasets, tested on the Reference dataset

For each DoC-dataset, we trained a PLS model, including those spontaneous EEG features showing significant univariate classification, according to the *neuro-behavioural* scheme. For this scheme, UWS_Hi^{PCI} patients were never included in any training set, and thus, they did not bias the model's estimates of the capacity for consciousness. Each model's performance was tested in the same DoC dataset and validated in the Reference dataset. This revealed the potential to estimate the capacity for consciousness within a specific DoC dataset (resubmit performance) and its generalization to controlled reference conditions.

Cross-validation on the merged datasets

Furthermore, we merged the datasets where a model showed consistent generalization and evaluated the overall performance by repeated stratified cross-validation (see Supplementary Material S2.5). This strategy allowed us to observe if the spontaneous EEG predictors aligned with the proposed *neuro-behavioural* stratification across a wide range of brain states, including DoC and Reference datasets.

Finally, to evaluate the sensitivity of the *neuro-behavioural* PLS model at a single cutoff, we thresholded the PLS regression values (in each cross-validation run). Since the *neuro-behavioural* scheme accounts for the capacity for consciousness during unresponsiveness, the threshold was set at the maximum of the unconscious class (NB−), corresponding to *specificity* = 1.

Correlations with PCI

We assessed the correlation across participants (Pearson's *R*) between the spontaneous EEG predictors (univariate or multivariate) and the complexity of the TMS-evoked EEG responses (PCI-max), in each dataset (Fig. 7). To avoid a leverage bias, UWS_0^{PCI} patients—all having the same PCI value by definition—were excluded from this analysis. To further assess this relationship across all patients, including those with 0^{PCI}, we accordingly performed Spearman's correlations, which considered tied-ranks (Supplementary Table 5). Bonferroni–Holm correction was applied to the *P*-values, according to the number of predictors (univariate or multivariate) assessed in each dataset.

Data availability

Raw EEG signals of neurotypical subjects during wakefulness and anesthesia are available at the repository Zenodo (10.5281/

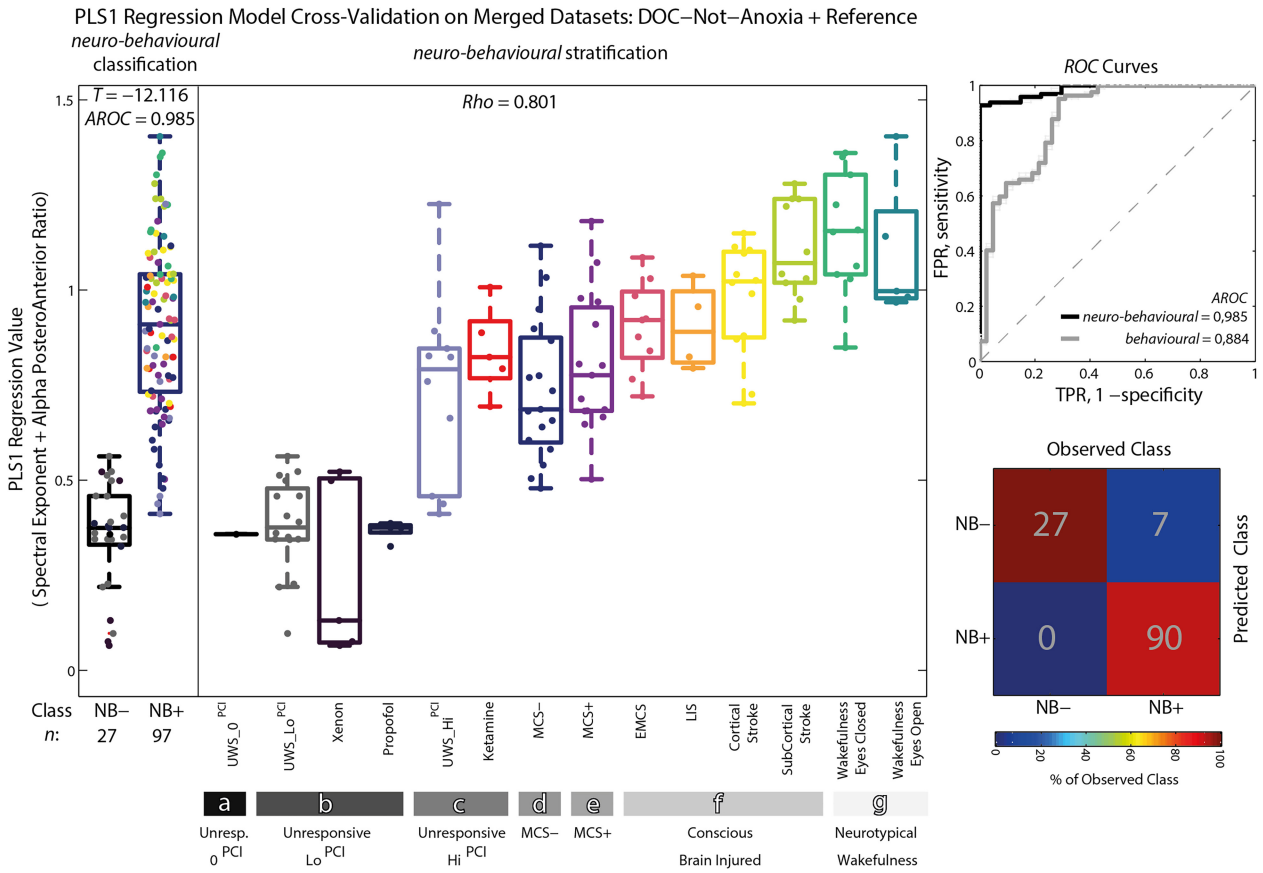

Fig. 6. The bivariate model was cross-validated on the Reference and DoC-Not-Anoxia dataset merged together; its predictions highly align with the *neuro-behavioural* stratification, consistently across traumatic and vascular brain injury, anesthesia, and neurotypical wakefulness. The bivariate model, combining the Spectral Exponent and the Alpha Postero-anterior ratio into a single partial least square component (PLS1), was cross-validated on the merged datasets (DoC-Not-Anoxia + Reference). The bivariate model was highly predictive of the capacity for consciousness; the resulting regression values were highly aligned with the proposed *neuro-behavioural* stratification (Fig. 2), as revealed by high *Rho* values from Spearman's rank-correlations. Statistics reported are averages across the cross-validation repetitions. The model's predicted value shown for each individual (colored dot) is the average across all the validation/test folds and repetitions, thus avoiding the bias of including the same datapoint in the train- and test-set. Top right, the *ROC* curve is shown in thin light gray for each repetition of the cross-validation, and the median is shown in thick stroke (black for *neuro-behavioural*, gray for *behavioural* scheme). An empirical threshold was derived to maximize specificity in each cross-validation run, yielding discrete predictions on the capacity for consciousness (*neuro-behavioural* scheme). Bottom right, the confusion matrix displays the absolute number of individuals, averaged across the cross-validation runs, in each quadrant; the percentage of individuals relative to those in the real class is color-coded. Targeting for maximal specificity yielded nonetheless an excellent sensitivity (90/97, 92.78% throughout cross-validation runs).

zenodo.806176). Further data are available upon reasonable request, following a data sharing agreement with the two research groups that collected the data: (i) Dipartimento di Scienze Biomediche e Cliniche, Università Degli Studi di Milano (89 recordings), and (ii) Coma Science Group, GIGA-Consciousness, University of Liège and Centre du Cerveau2, University Hospital of Liège (33 recordings). Anesthesia data (30 recordings) were jointly collected by both research groups.

Results

PCI specifies the lower end of the prior *neuro-behavioural* scheme

A cross-tabulation of the patients' *neuro-behavioural* group and aetiology is depicted in Supplementary Fig. 2. See Supplementary Material for detailed PCI results (Supplementary Material S3.1, Supplementary Fig. 3). Briefly, PCI predicted the capacity for consciousness in 8/8 MCS and in 2/20 UWS patients of the DoC-Anoxia dataset and in 30/32 MCS and in 10/27 UWS patients of the DoC-Not-Anoxia dataset. Patients with no EEG response to TMS were all UWS, and primarily anoxic (12/13 UWS_0^{PCI}, Fig. 2). Furthermore, PCI correctly identified the presence/absence of consciousness (respectively 55 and 10) in all cases of the Reference dataset.

Univariate results

In each dataset, we assessed whether spontaneous EEG predictors could classify the presence/absence of the capacity for consciousness (classification, *AROC*, *T*-values) and to stratify patients in agreement with the prior *neuro-behavioural* stratification (stratification, Spearman's *Rho*). We also assessed the correlation (Pearson's *R*) across subjects of the spontaneous-EEG features with PCI-max (Fig. 7). First, classification, stratification, and correlation were performed for each univariate feature (Table 1, Supplementary Table 2; *neuro-behavioural* results in Fig. 4, *behavioural* results in Supplementary Fig. 5). The main results observed in the entire DoC-Not-Anoxia dataset were also consistently observed when vascular and traumatic patients were considered separately (Supplementary Fig. 4, Supplementary Material S3.3).

Briefly, Alpha Power was markedly suppressed only among unconscious anoxic patients (in UWS_Lo^{PCI}, and maximally in UWS_0^{PCI}); thus, it distinguished the un/conscious class in the

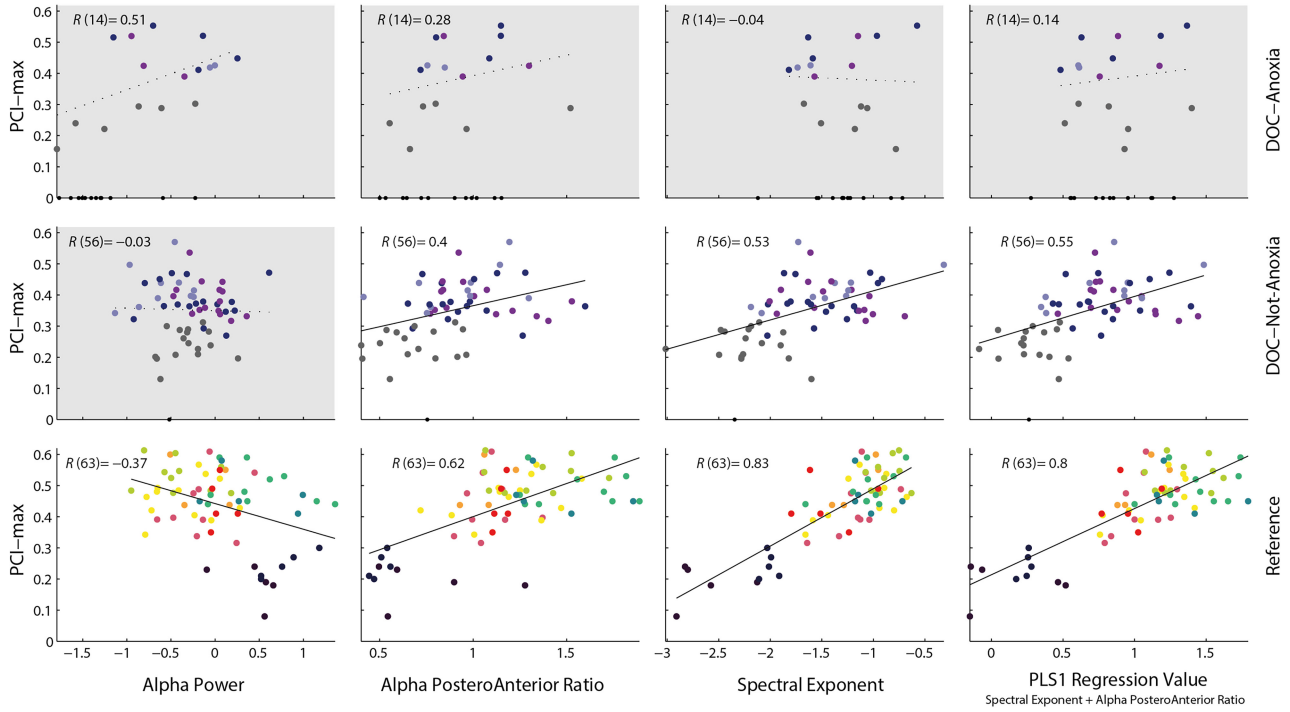

Fig. 7. Alpha Postero-Anterior Ratio and Spectral Exponent, as well as their bivariate combination, correlated with PCI-max, in both the DoC-Not-Anoxia and in the Reference dataset. Features derived from the spontaneous-EEG were correlated across subjects with PCI-max (individual's best value of the PCI, obtained from TMS-evoked EEG responses) by means of Pearson's correlation, resulting in *R* values. Results were similar for the Spectral Exponent, for the Alpha Postero-Anterior Ratio, and for their bivariate combination, obtained by the partial least square regression model with 1 component (PLS1), trained on the DoC-Not-Anoxia dataset. The correlation between these values and PCI-max was positive in the Reference dataset and in the DoC-Not-Anoxia dataset, yet absent in the DoC-Anoxia dataset. The correlation between Alpha Power and PCI-max was negative in the Reference dataset, positive albeit not significant in the DoC-Anoxia dataset, and absent in the DoC-Not-Anoxia dataset. *P*-values (raw and corrected) are reported in Supplementary Table 5. Patients with 0^{PCI} are displayed (small black dots aligned on 0 on the Y coordinate) but excluded from correlation analysis (note: these were included in Spearman correlation analysis, reported in Supplementary Table 5).

DoC-Anoxia dataset and did not correlate with PCI values (but see Supplementary Table 5). Such associations were not found in the DoC-Not-Anoxia dataset, whereas a negative association was found in the Reference dataset (during Xenon and Propofol anesthesia, Alpha Power was sustained to wakefulness levels). Furthermore, Alpha Power positively correlated with the *neuro-behavioural* stratification in the DoC-Anoxia dataset, and to a lesser extent, in the DoC-Not-Anoxia dataset.

Both Spectral Exponent and Alpha Postero-Anterior Ratio (mutually correlated across datasets, Supplementary Fig. 7) discriminated consciousness and correlated with the *neuro-behavioural* stratification and PCI values in both the DoC-Not-Anoxia and Reference datasets, but not in the DoC-Anoxia dataset (details in Supplementary Material S3.4). Univariate results are detailed further in Supplementary Material (S3.2).

Multivariate results

Bivariate DoC models and their validation on the Reference dataset

We trained a bivariate PLS regression model to predict the presence/absence of the capacity for consciousness in each DoC dataset, according to the *neuro-behavioural* scheme. We selected the features with significant univariate classification performance (Fig. 4), z-scored them, and combined them into a single PLS component (see Methods). In the DoC-Anoxia dataset, only Alpha Power showed significant univariate performance, and thus, the PLS model—being analogous to univariate analysis—was not further explored. The DoC-Not-Anoxia model combined the Spectral Exponent (PLS slope of regression, $\beta = 0.239$) and the Alpha Postero-Anterior Ratio ($\beta = 0.185$; details in Supplementary Table 3, Supplementary Material S3.6.1). This bivariate model classified the capacity for consciousness in most cases of the DoC-Not-Anoxia dataset and generalized to all cases of the Reference dataset but did not so in the DoC-Anoxia dataset (Fig. 5, Table 1). In addition, the PLS regression values of the bivariate DoC-Not-Anoxia model robustly correlated with the *neuro-behavioural* stratification, both in the DoC-Not-Anoxia and in the Reference dataset, but not in the DoC-Anoxia dataset. For the *neuro-behavioural* scheme, we thresholded predictions values into a discrete classification; targeting for maximal specificity still resulted in high sensitivity in the DoC-Not-Anoxia dataset (35/42, 83.33%) and maximal in the Reference dataset (55/55, 100%), thus generalizing across traumatic/vascular brain injuries, neurotypical wakefulness, and anesthesia (details in Supplementary Material S3.5).

Cross-validation of the bivariate model in the merged datasets

Subsequently, to observe if the proposed *neuro-behavioural* stratification aligned with the spontaneous-EEG statistical predictions across a wide range of brain states, we merged the datasets where a PLS model could show consistent generalization. Accordingly, the Doc-Not-Anoxia model (combining Spectral Exponent and Alpha Postero-Anterior Ratio; details in Supplementary Material S3.6.2 and Supplementary Table 4) was cross-validated on the DoC-Not-Anoxia and the Reference dataset merged together, to predict the capacity for consciousness (*neuro-behavioural* classification; Fig. 6), or Behavioral responsiveness for comparison.

This bivariate model could predict the capacity for consciousness in the vast majority of cases, and the resulting regression values were highly correlated to the *neuro-behavioural* stratification, across behaviourally (un)responsive patients with brain injuries of traumatic/vascular aetiology, and neurotypical individuals during wakefulness and different anesthetic conditions. In this challenging context, a binary classification targeting for maximal specificity (threshold: average = 0.557, SD = 0.005) yielded an excellent sensitivity (90/97 correct cases; 7/97 incorrect cases, of which 3 UWS_Hi^{PCI}, 3 MCS−, and 1 MCS+ patients), consistently in all rounds of cross-validation (Fig. 6).

Discussion

Here, we first evaluated whether alpha power suppression could particularly index severe diffuse cortical postanoxic damage rather than unconsciousness per se, and second, whether the alteration of spatial and spectral gradients could stratify patients with DoC and classify their capacity for consciousness. EEG-based stratification and classification was contrasted to a here-developed *neuro-behavioural* scheme (Fig. 2), integrating behavioural assessments with an independent reliable neural marker of consciousness, i.e. PCI. Finally, to assess the validity of diagnostic indexes as markers of consciousness, we evaluate whether findings could generalize to the known conditions of the Reference dataset.

We observed a marked suppression of Alpha Power only among severe postanoxic patients (UWS with Lo^{PCI}, and particularly in UWS with 0^{PCI}, i.e. absent EEG responses to TMS, Fig. 4), in the context of an overall power suppression (low-voltage, Figs 1 and 3, and Supplementary Fig. 6). Yet, Alpha Power could not index the capacity for consciousness in not-anoxic DoC patients, and it did not generalize to the Reference dataset, revealing instead an opposite pattern whereby Alpha Power was sustained to wakefulness levels during anesthetic-induced unconsciousness (Xenon, Propofol). Thus, Alpha Power could reliably index the overall suppression of cortical activity (reflected by the low-voltage pattern and the absence of reactivity to direct cortical perturbations) typical of severe diffuse postanoxic damage, rather than the absence of consciousness.

Viceversa, spatial and spectral gradients—indexed by the Alpha Postero-Anterior Ratio and the Spectral Exponent—robustly stratified patients with not-anoxic DoC and discriminated their capacity for consciousness while robustly generalizing to pharmacological and neurological conditions of the Reference dataset (Fig. 4). However, the two features were not reduced in the specific case of severe anoxic DoC patients, due to the overall marked suppression of the neurogenic signal below the level of peripheral artifacts (Supplementary Material and Supplementary Fig. 6) masking expected differences in spatial and spectral gradients. The two features were subsequently combined in a bivariate index, improving classification and stratification performance in the DoC-Not-Anoxia dataset, and in the generalization to the Reference dataset (Fig. 5), reaching excellent performance across the two datasets (Fig. 6).

Alpha power suppression reflects severe diffuse brain damage

Severe postanoxic damage led to EEG low-voltage—a broad-band power suppression—and predominantly arrhythmic activity (Figs. 1A and 3 and Supplementary Fig. 6)—in line with previous findings (Hockaday et al. 1965; Estraneo et al. 2016; Hofmeijer and van Putten 2016; Rossetti et al. 2016; Snider et al. 2022). This overall suppression of cortical activity was most evident as a marked alpha power suppression (Figs. 3 and 4), partially because this frequency range is inherently less confounded by artifacts (low-frequency ocular activity and high-frequency muscular activity). According to a visual categorization of EEG in DoC, alpha power suppression and arrhythmic activity characterize the "A"-type EEG (Schiff 2016), a pattern that may represent diffuse thalamocortical damage and complete loss of structural integrity, typical of severe postanoxic UWS patients (Forgacs et al. 2017).

Here, Alpha Power was suppressed only among severe postanoxic UWS patients (Fig. 4). In particular, suppressed Alpha Power (i.e. a ∼1.7 median reduction in Alpha Power relative to healthy waking participants, yielding negligible values) was consistently observed among patients with no EEG response to TMS (0^{PCI}), a group primarily represented by anoxic aetiology (12/13). As previously suggested, 0^{PCI} may signal the absence of cortical reactivity, thereby consistent with a severe diffuse cortical damage and thus unconsciousness (Casarotto et al. 2016). Conversely, in the DoC-Not-Anoxia dataset, Alpha Power was not suppressed among UWS patients (Figs. 1, 3 and 4), and Alpha Power was related to responsiveness (i.e. *behavioural* classification; Supplementary Fig. 5) rather than the capacity for consciousness (Fig. 4, Supplementary Fig. 4).

Among multiple spectral, information-theoretic, and connectivity features, absolute alpha power showed the highest diagnostic performance in discriminating UWS from MCS patients in previous large studies (Sitt et al. 2014; Engemann et al. 2018) and strongly influenced the ensemble classifier decisions (Engemann et al. 2018). Yet, the present findings suggest that this performance may be conflated by the high prevalence of anoxic aetiology in the UWS population and by the adoption of a behavioural classification. Thus, training a model on a dataset where anoxic patients are significantly represented would lead to attribute importance to features strongly influenced by EEG low-voltage, most notably alpha power, that may be detrimental for the classification of the capacity for consciousness in not-anoxic patients. This bias could apply to the prolonged/chronic phases as well as to the early phases of DoC (Sitt et al. 2014; Engemann et al. 2018; Amiri et al. 2022). When evaluating the diagnostic and prognostic value of EEG features influenced by band-power suppression, future studies should consider anoxic and non-postanoxic DoC patients separately (Estraneo et al. 2016).

Moreover, Alpha Power in the Reference dataset varied in contrast to the capacity for consciousness—irrespectively of *behavioural* responsiveness. During anesthetic-induced unconsciousness (Xenon and Propofol conditions), Alpha Power was sustained to wakefulness levels, as previously reported (Laitio et al. 2008; Purdon et al. 2015; Scheinin et al. 2018; Pelentritou et al. 2020). On the flip side, during Ketamine anesthesia, consciousness was retained—albeit dissociated from environmental inputs—while Alpha Power was attenuated, as previously reported (Akeju et al. 2016; Vlisides et al. 2017). Furthermore, serotonergic psychedelic substances (e.g. LSD, Psilocin, Dimethyltryptamine) markedly reduce alpha power (Rodin and Luby 1966; Muthukumaraswamy et al. 2013; Schartner et al. 2017; Muthukumaraswamy and Liley 2018; Timmermann et al. 2019), yet despite phenomenological changes, consciousness is retained (Millière et al. 2018). Further supporting the notion that alpha activity may not reflect the presence of consciousness, we found reduced Alpha Power in conscious patients with LIS (Fig. 4), consistently with previous reports (Babiloni et al. 2010). Finally, healthy conscious individuals can completely lack resting alpha oscillations, due to a rare condition known as "Low-voltage alpha

EEG" (Vogel 1970; Anokhin 2014). All of the above challenges the recently proposed notion that alpha activity is "the rhythm of a conscious brain" (Sokoliuk and Cruse 2018).

Overall, alpha power cannot be a general marker of consciousness, given the absence of a consistent relationship with the capacity for consciousness across patients with not-anoxic brain-injury, and neurotypical individuals during wakefulness and multiple anesthetic conditions. Among brain-injured patients, alpha power suppression was often associated with absent reactivity to direct cortical perturbations and may index profound loss of thalamocortical integrity, typical of severe diffuse postanoxic injury.

Anteriorization and the loss of consciousness

While the alpha gradient was disorganized across most postanoxic patients—irrespectively of the presence of consciousness—it indexed unconsciousness and correlated with the *neuro-behavioural* stratification both in the DoC-Not-Anoxia and in the Reference dataset. More specifically, besides variations in global Alpha Power, the alpha gradient progressively normalized from UWS_Lo^{PCI} to MCS+ in the DoC-Not-Anoxia dataset and markedly reversed during Xenon and Propofol anesthesia (Fig. 4). Consistently, alpha anteriorization is typically associated to the loss of consciousness, irrespectively of its origin, either physiological (De Gennaro et al. 2001; Ogilvie 2001), pharmacological (Ching et al. 2010; Vijayan et al. 2013; Purdon et al. 2015; Scheinin et al. 2018), or neurological (Scollo-Lavizzari and Bassetti 1987; Synek 1988; Berkhoff et al. 2000; Estraneo et al. 2016). Alterations of the neurotypical postero-anterior gradient could result either from an anterior increase or a posterior decrease in alpha power (Hirsch et al. 2021). The first may be explained by a potentiation of the inhibitory drive (GABA A) that synchronizes frontal thalamocortical circuits in the alpha frequency range; the second may arise from decreased thalamic drive to the occipital cortex (Vijayan et al. 2013).

EEG slowing and the loss of consciousness

In patients with vascular or traumatic aetiology included in our DoC-Not-Anoxia dataset—where focal or multifocal brain lesions coexist with structurally preserved areas–broad-band slowing (measured by the Spectral Exponent, Fig. 1) reliably indexed the presence of consciousness and stratified patients in agreement with the *neuro-behavioural* stratification (Fig. 4; supplementary Fig. 4). A similar relation was found in general anesthesia—where functional disconnection occurs in a structurally preserved brain. This relationship was absent in anoxic patients though, where the Spectral Exponent was relatively unaltered. Indeed, diffuse and severe anoxic damage leaves little to no structurally preserved cortical tissue able to generate neurogenic signal (as indexed by suppressed broad-band and alpha-band power; Figs 3 and 4 and Supplementary Fig. 6), thus lowering the signal to noise ratio of neuronal to myogenic activity (see Supplementary Material). Similarly, in a recent study during acute coma following cardiac arrest, the broad-band Spectral Exponent was not different from healthy controls (Alnes et al. 2021).

The present findings are consistent with the notion that slow waves emerge in structurally preserved cortical tissue suffering from (partial) deafferentation (Sanchez-Vives and McCormick 2000; Timofeev 2000). Controlled focal brain lesions generate slowing in areas connected to the lesion (Gloor et al. 1977), as revealed by intracranial human recordings (Russo et al. 2021). In cats, cortical slowing appears with the interruption of afferences, either by white matter, thalamic, hypothalamic, or brainstem lesions (Gloor et al. 1977). In DoC patients, EEG slowing correlated with thalamic atrophy, implying that cortical slowing follows the damage of diffuse thalamocortical projections (Lutkenhoff et al. 2022). Furthermore, hemispheric slowing—measured by the Spectral Exponent—identified the affected hemisphere of stroke patients and negatively predicted functional recovery (Lanzone et al. 2022). Overall, loss of consciousness in nonanoxic DoC (and anesthesia conditions) was significantly associated to EEG slowing, likely generated by (functionally/structurally) deafferented, yet intact, cortical tissue.

Spectral exponent, PCI, and the propagation of cortical activity

More negative Spectral Exponent values, indexing broad-band slowing and steeper PSD decay, predicted unconsciousness and lower PCI values across a wide range of conditions, including focal/multifocal brain injuries, neurotypical wakefulness, and different anesthetics (Figs 3, 4, and 7). Spectral Exponent and PCI capture separate aspects of brain activity (spontaneous and TMS-evoked, respectively), hence their correlation is intriguing. Their relationship may be explained by mechanisms regulating the propagation/extinction of cortical activity. Specifically, steeper PSD decay has been associated with lower excitation-inhibition ratio of synaptic activity (Gao et al. 2017), longer lasting inhibitory postsynaptic potentials, and lower firing rate (Brake et al. 2021). Near the critical transition between activity propagation and extinction, neural activity becomes maximally integrated and differentiated across areas (Tagliazucchi 2017). The criticality framework offers a mechanistic explanation for the joint emergence of consciousness and integrated information (Kim and Lee 2019; Lee et al. 2019). Thus, the critical regime may provide an optimal condition to obtain high complexity of TMS-evoked EEG activity, a key property of conscious states (Casali et al. 2013; Casarotto et al. 2016). Conversely, the prevalence of extinction over propagation mechanisms entails low PCI values—corresponding to less complex, more stereotypical and/or spatially constrained responses, typical of unconsciousness. Supporting this view, a reduction in network criticality and a steeper PSD decay were jointly observed during propofol-induced loss of consciousness (Maschke et al. 2022; Toker et al. 2022). In sum, the balance between propagation and extinction of cortical activity may underlie the observed relation between the PSD decay, PCI values, and capacity for consciousness.

Blocking activity propagation: a pathway to unconsciousness, yielding slowing, and anteriorization

The Spectral Exponent and the Alpha Postero-Anterior Ratio were mutually correlated across neurotypical wakefulness, pharmacological, and neurological alterations of consciousness (Supplementary Fig. 7) and—except for anoxic aetiology—decreased together as a function of the *neuro-behavioural* stratification (Fig. 4). Coherently, in other neurological conditions such as hepatic encephalopathy, slowing and alpha anteriorization co-occurred with increasing severity of symptoms, ranging from mild impairment to coma (Olesen et al. 2016). Given that the two features are methodologically unrelated, this correlation may reflect a single underlying neurobiological mechanism. Indeed, both effects were jointly obtained by progressively blocking activity propagation, in a simple neuropercolation model of general anesthesia (Zhou et al. 2015). In this study, the wakefulness model was initialized with the biological constraint of predominant feedback connectivity. The progressive stochastic

disruption of neural connections yielded an increase in low-frequency activity; furthermore, by predominantly affecting feedback connectivity, it also yielded the anteriorization of delta and alpha activity. Despite its simplicity, this coarse-grained model provides evidence that the blockage of activity propagation may represent a general principle linking EEG slowing, anteriorization, and loss of consciousness.

Bivariate DoC model, validation in the Reference dataset and stratification in the merged datasets

To predict the capacity for consciousness, we trained a linear PLS model in each DoC dataset, selecting features based on univariate results. Hence, the DoC-Not-Anoxia model combined the Spectral Exponent with the Alpha Postero-Anterior Ratio. While this model could not extend to the Doc-Anoxia dataset—where only Alpha Power showed significant performance—this model performed well in the DoC-Not-Anoxia and optimally generalized to the Reference dataset. Based on these results, we cross-validated this bivariate model across the DoC-Not-Anoxia and the Reference datasets merged together. The model's predictions were in large agreement with the *neuro-behavioural* stratification, across datasets including patients with traumatic or vascular brain-injury (either DoC or functionally communicating), as well as healthy individuals during wakefulness and under different anesthetics. In all these conditions, unconsciousness and lower ranks in the *neuro-behavioural* stratification were predicted by broad-band slowing together with alpha anteriorization. Specifically, both univariate (Fig. 4, Table 1) and bivariate analysis (Supplementary Tables 3 and 4) revealed that the strongest effects were observed for the Spectral Exponent.

A parsimonious model, disadvantages and advantages

Previous studies have shown that the combination of several EEG features in multivariate models can provide useful diagnostic indices for DoC (Sitt et al. 2014; Noirhomme et al. 2017; Engemann et al. 2018; Corchs et al. 2019; Amiri et al. 2022). Particularly, a recent ensemble model combining dozens of EEG features could discriminate UWS from MCS patients with good performance and was more robust to data corruption than univariate markers (Engemann et al. 2018). However, the cross-validated performance of the multivariate model was not superior to that afforded by absolute alpha power alone, as reported in the supplementary material of the paper (Engemann et al. 2018). Notably, alpha power likely reflects thalamocortical integrity rather than indexing consciousness, as revealed by our observations and discussed above. At the same time, the combination of several markers across recording paradigms and neuroscientific tools does not necessarily improve diagnostic performances in DoC (Hermann et al. 2021; Amiri et al. 2022). Finally, the neurophysiological insights of these multivariate models are inherently limited by the large number of features influencing diagnosis, and by multiple levels of nonlinearity (James et al. 2013; Noirhomme et al. 2017).

Here, rather than combining a multitude of EEG features or multimodal measures by elaborate machine learning architectures, which may remain opaque to clinical understanding, we chose a model based on few clinically relevant and pathophysiologically informed EEG features. This approach resulted in a parsimonious and interpretable regression model, which was highly predictive of the capacity for consciousness in not-anoxic patients, correlated with the *neuro-behavioural* stratification, and generalized to reference conditions. This result, although potentially surprising at first, is conceivable given that disparate EEG features tend to be interdependent (e.g. Supplementary Fig. 7), that visual analysis of EEG in DoC relies on the combination of a rather small set of criteria (Forgacs et al. 2014; Estraneo et al. 2016), and that even the multivariate ensemble model for DoC can actually be driven by few markers, such as absolute alpha power (Engemann et al. 2018).

Neuro-behavioural scheme, a step toward an unobservable ground truth

Predictions from the spontaneous EEG showed an overall larger agreement with the *neuro-behavioural* scheme—in alignment with PCI results (Casarotto et al. 2016)—with respect to the purely *behavioural* scheme (Figs 4–6, Supplementary Fig. 5; Table 1 and Supplementary Table 2). This supports the notion that spontaneous EEG predictions can index the capacity for consciousness, going beyond behavioural responsiveness per se (Chennu et al. 2017; Candia-Rivera et al. 2021). Since the *neuro-behavioural* scheme contemplates the capacity for consciousness during unresponsiveness, we set the empirical threshold to exclude any false positives. Targeting for such maximal specificity, still resulted in high sensitivity in the Doc-Not-Anoxia (83.33%) and Reference dataset (100%). Further empirical studies are warranted to refine such threshold.

Of relevance, our study confirms the notion that a well-preserved EEG is compatible with covert consciousness (Forgacs et al. 2014) and provides both a quantification and a model that allows a graded stratification across a wide range of conditions including neurotypical wakefulness, general anesthesia, multifocal, and focal brain-injury, as well as DoC of traumatic or vascular aetiology. In practice, considering specificity (100%), a positive EEG prediction should be taken as an indication of preserved capacity for consciousness, thus calling for intensive therapeutic efforts aimed at restoring functional communication, especially in the early rehabilitation phases (Comanducci et al. 2020). Conversely, considering sensitivity (83.33%), a negative EEG prediction warrants further assessments to reduce misdiagnosis, similarly to the recommendations for the CRS-R (Wannez et al. 2017) and to the European and American Academy of Neurology guidelines (Giacino et al. 2018b; Kondziella et al. 2020). In this case, a diagnostic tool with even higher sensitivity, such as PCI (Casarotto et al. 2016), could potentially reveal "islands of high-complexity" (Bayne et al. 2020). Hence, our informed quantitative approach to spontaneous-EEG may constitute a widely available, reliable first-step screening at the bed-side, that well fits with the flowchart of diagnostic assessment in DoC (Comanducci et al. 2020, Fig. 9 therein).

Limitations

Misdiagnosis can result from the important daytime arousal fluctuations typical of DoC patients, affecting both behaviour and EEG activity (Piarulli et al. 2016; Mertel et al. 2020). It is thus crucial to minimize the intrusion of sleepiness during EEG recording and preprocessing.

Furthermore, common biological artifacts may affect EEG-derived metrics. For instance, ocular and muscular artifacts, respectively, increase low- and high-frequency power, disproportionately affecting the EEG when the neurogenic signal is suppressed, as in severe anoxic patients (Supplementary Material S3.7). Artifact correction procedures (such as ICA cleaning applied here, Supplementary Material S2.4) are needed to minimize these

sources of bias, although the practice is not common in the field of EEG in DoC (Corchs et al. 2019). It will be crucial to adapt the procedures for standard clinical EEG recordings equipped with less electrodes.

Here, we did not focus on the effects of time from injury. Instead, we focused on diagnostic capacity of EEG features; accordingly, our dataset is mostly represented by prolonged/chronic patients, whose diagnosis is relatively stable over time (Supplementary Material). In our dataset, there was only a marginal effect on EEG features directly attributable to time from injury, and the main results were not affected by it (Supplementary Material). Yet, time from injury may play a role in the early phases that follow brain-injury, where EEG features and diagnosis are more likely to evolve. In acute patients, time of injury can be predictive of the amount of alpha power, particularly so for anoxic patients. Interestingly, prominent alpha power was predictive of favorable outcome, during the first day of coma (Kustermann et al. 2019). Future studies, particularly longitudinal ones in acute settings, are warranted to assess the influence of time from injury on EEG features.

Conclusions

Our findings revealed that alpha power is not a general marker of consciousness; rather, alpha suppression indexes the overall suppression of cortical activity typical of diffuse severe postanoxic injury. Such an instance represents a special adverse case, with markedly different pathophysiology, which if not properly accounted for, may confound the evaluation of DoC in traumatic and vascular aetiology. Moving beyond alpha power, we based our approach on few clinically relevant and pathophysiologically informed EEG features, reflecting slowing and anteriorization, in contrast to more elaborate yet more opaque machine learning tools. This approach provides a robust, generalizable, and parsimonious index of the capacity for consciousness, whose application in the clinic may allow better resource allocation and individualized rehabilitation strategies.

Acknowledgments

Thanks to all the patients and volunteers who made this work possible. Many thanks to dr. Andrea Pigorini, for developing graphical ideas, to dr. Ezequiel Mikulan and to Renzo Comolatti, for invaluable statistical advice, and to Simone Russo, for precious comments during the writing process. Heartfelt thanks to the lab members who contributed to data collection and conceptualization of the study, and to all the newer and former lab members for providing a friendly and inspiring atmosphere. Further, M.C. wishes to thank dr. Sasha Ambrosio for hardware support and stimulating conversations, to MD Favaro Jacopo for the resilient collaboration, and dr. Grade Tardi for inspiring patience and endurance. Many thanks to all members of the Liege department of anaesthesia and of the Coma Science Group, and in particular to dr. Rajanikant Panda, dr. Aurore Thibaut, Paolo Cardone and Benedetta Cecconi. Thanks to MD Cristina Landi and MD Guya Devalle for patient assessment. Thanks to MD Francesca Baglio for neuroimaging that allowed TMS neuro-navigation in some patients.

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Funding

European Union's Horizon 2020 Framework Program for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3) (to MM, MR, and SL); Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), Project PerBrain, call ERAPERMED2019–101, GA 779282 (to MR and AC); Italian Ministry of Health ("Ricerca Corrente 2022") to AC, CD, and AM; Tiny Blue Dot Foundation (to MM); Belgian National Funds for Scientific Research (F.R.S-FNRS; to SL and OG); Fondazione Europea di Ricerca Biomedica (to SL); BIAL Foundation (to SL and OG); AstraZeneca (to OG); Foundation Roi Baudouin (to SL); Italian Ministry of Health, GR – 2016–02361494 (to SC); Fondazione Fratelli Giuseppe Vitaliano, Tullio e Mario Confalonieri (to MAC).

Conflict of interest statement: MM is co-founder of Intrinsic Powers, a spin-off of the University of Milan; SS, MR, and SC are advisors of Intrinsic Powers. The other authors report no competing interests.

Authors' contributions

Michele A. Colombo (Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Angela Comanducci (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Resources, Writing—original draft, Writing—review & editing), Silvia Casarotto (Data curation, Formal analysis, Funding acquisition, Investigation, Resources), Chiara-Camilla Derchi (Data curation, Formal analysis, Investigation), Jitka Annen (Data curation, Investigation), Alessandro Viganò (Investigation, Writing—review & editing), Alice Mazza (Investigation), Davide P. Trimarchi (Investigation), Mélanie Boly (Investigation), Matteo Fecchio (Investigation), Olivier Bodart (Investigation), Jorge Navarro (Project administration, Resources), Steven Laureys (Funding acquisition, Project administration, Resources), Olivia Gosseries (Data curation, Funding acquisition, Investigation, Project administration), Marcello Massimini (Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing), Simone Sarasso (Conceptualization, Data curation, Investigation, Supervision, Writing—original draft, Writing—review & editing), and Mario Rosanova (Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing).

References

Akeju O, Song AH, Hamilos AE, Pavone KJ, Flores FJ, Brown EN, Purdon PL. Electroencephalogram signatures of ketamine-induced unconsciousness. *Clin Neurophysiol*. 2016:127(6): 2414–2422. https://doi.org/10.1016/j.clinph.2016.03.005.

Alnes SL, De LM, Rossetti AO, Tzovara A. Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma. *NeuroImage*. 2021: 245:118638. https://doi.org/10.1016/j.neuroimage.2021.118638.

Amiri M, Fisher PM, Raimondo F, Sidaros A, Hribljan MC, Othman MH, Zibrandtsen I, Albrechtsen SA, Bergdal O, Hansen AE et al. Multimodal prediction of residual consciousness in the intensive care unit: the CONNECT-ME study. *Brain*. 2022. https://doi.org/10.1093/brain/awac335.

Anokhin AP. Genetic psychophysiology: advances, problems, and future directions. *Int J Psychophysiol*. 2014:93(2):173–197. https://doi.org/10.1016/j.ijpsycho.2014.04.003.

Babiloni C, Pistoia F, Sarà M, Vecchio F, Buffo P, Conson M, Onorati P, Albertini G, Rossini PM. Resting state eyes-closed cortical rhythms in patients with locked-in-syndrome: an eeg study. *Clin Neurophysiol*. 2010:121(11):1816–1824. https://doi.org/10.1016/j.clinph.2010.04.027.

Bagnato S, Boccagni C, Santangelo A, Prestandrea C, Mazzilli R, Galardi G. EEG predictors of outcome in patients with disorders of consciousness admitted for intensive rehabilitation. *Clin Neurophysiol*. 2015:126(5):959–966. https://doi.org/10.1016/J.CLINPH.2014.08.005.

Bai Y, Xia X, Li X. A review of resting-state electroencephalography analysis in disorders of consciousness. *Front Neurol*. 2017:8(SEP):471. https://doi.org/10.3389/fneur.2017.00471.

Baird B, Castelnovo A, Riedner BA, Lutz A, Ferrarelli F, Boly M, Davidson RJ, Tononi G. Human rapid eye movement sleep shows local increases in low-frequency oscillations and global decreases in high-frequency oscillations compared to resting wakefulness. *eNeuro*. 2018:5(4). https://doi.org/10.1523/ENEURO.0293-18.2018.

Bauer G, Trinka E, Kaplan PW. EEG patterns in hypoxic encephalopathies (post–cardiac arrest syndrome). *J Clin Neurophysiol*. 2013:30(5):477–489. https://doi.org/10.1097/WNP.0b013e3182a73e47.

Bayne T, Seth AK, Massimini M. Are there islands of awareness? *Trends Neurosci*. 2020:43(1):6–16. https://doi.org/10.1016/j.tins.2019.11.003.

Benca RM, Obermeyer WH, Larson CL, Yun B, Dolski I, Kleist KD, Weber SM, Davidson RJ. EEG alpha power and alpha power asymmetry in sleep and wakefulness. *Psychophysiology*. 1999:36(4):430–436. https://doi.org/10.1111/1469-8986.3640430.

Berkhoff M, Donati F, Bassetti C. Postanoxic alpha (theta) coma: A reappraisal of its prognostic significance. *Clin Neurophysiol*. 2000:111(2):297–304. https://doi.org/10.1016/S1388-2457(99)00246-1.

Bernat JL. Chronic disorders of consciousness. *Lancet*. 2006:367(9517):1181–1192. https://doi.org/10.1016/S0140-6736(06)68508-5.

Brake N, Duc F, Rokos A, Arseneau F, Shahiri S, Plourde G. Aperiodic EEG activity masks the dynamics of neural oscillations during loss of consciousness from propofol. bioRxiv2021 October 12.464109. 2021: 10.1101/2021.10.12.464109.

Candia-Rivera D, Annen J, Gosseries O, Martial C, Thibaut A, Laureys S, Tallon-Baudry C. Neural responses to heartbeats detect residual signs of consciousness during resting state in postcomatose patients. *J Neurosci*. 2021:41(24):5251–5262. https://doi.org/10.1523/JNEUROSCI.1740-20.2021.

Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, Casarotto S, Bruno M-A, Laureys S, Tononi G et al. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med*. 2013:5(198):198ra105–198ra105. https://doi.org/10.1126/scitranslmed.3006294.

Casarotto S, Comanducci A, Rosanova M, Sarasso S, Fecchio M, Napolitani M, Pigorini A, Casali A G, Trimarchi PD, Boly M et al. Stratification of unresponsive patients by an independently validated index of brain complexity. *Ann Neurol*. 2016:80(5):718–729. https://doi.org/10.1002/ana.24779.

Chennu S, Finoia P, Kamau E, Allanson J, Williams GB, Monti MM, Noreika V, Arnatkeviciute A, Canales-Johnson A, Olivares F, et al. 2014. Spectral signatures of reorganised brain networks in disorders of consciousness. Ermentrout B, editor. *PLoS Comput Biol*. 10(10):e1003887. 10.1371/journal.pcbi.1003887

Chennu S, Annen J, Wannez S, Thibaut A, Chatelle C, Cassol H, Martens G, Schnakers C, Gosseries O, Menon D et al. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. *Brain*. 2017:140(8):2120–2132. https://doi.org/10.1093/brain/awx163.

Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ. Thalamocortical model for a propofol-induced α-rhythm associated with loss of consciousness. *Proc Natl Acad Sci U S A*. 2010:107(52):22665–22670. https://doi.org/10.1073/pnas.1017069108.

Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJAM. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest. *Crit Care Med*. 2012:40(10):2867–2875. https://doi.org/10.1097/CCM.0b013e31825b94f0.

Colombo MA, Napolitani M, Boly M, Gosseries O, Casarotto S, Rosanova M, Brichant J-F, Boveroux P, Rex S, Laureys S 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. https://doi.org/10.1016/J.NEUROIMAGE.2019.01.024.

Comanducci A, Boly M, Claassen J, De Lucia M, Gibson RM, Juan E, Laureys S, Naccache L, Owen AM, Rosanova M et al. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. *Clin Neurophysiol*. 2020:131(11):2736–2765. https://doi.org/10.1016/j.clinph.2020.07.015.

Corchs S, Chioma G, Dondi R, Gasparini F, Manzoni S, Markowska-Kaczmar U, Mauri G, Zoppis I, Morreale A. Computational methods for resting-state EEG of patients with disorders of consciousness. *Front Neurosci*. 2019:13(JUL):807. https://doi.org/10.3389/fnins.2019.00807.

De Gennaro L, Ferrara M, Curcio G, Cristiani R. Antero-posterior EEG changes during the wakefulness-sleep transition. *Clin Neurophysiol*. 2001:112(10):1901–1911.

Engemann DA, Raimondo F, King J-R, Rohaut B, Louppe G, Faugeras F, Annen J, Cassol H, Gosseries O, Fernandez-Slezak D et al. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. *Brain*. 2018. https://doi.org/10.1093/brain/awy251.

Esposito MJ, Nielsen TA, Paquette T. Reduced alpha power associated with the recall of mentation from stage 2 and stage REM sleep. *Psychophysiology*. 2004:41(2):288–297. https://doi.org/10.1111/j.1469-8986.00143.x.

Estraneo A, Moretta P, Loreto V, Lanzillo B, Cozzolino A, Saltalamacchia A, Lullo F, Santoro L, Trojano L. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. *Neurology*. 2013:80(5):464–470. https://doi.org/10.1212/WNL.0b013e31827f0f31.

Estraneo A, Loreto V, Guarino I, Boemia V, Paone G, Moretta P, Trojano L. Standard EEG in diagnostic process of prolonged disorders of consciousness. *Clin Neurophysiol*. 2016:127(6):2379–2385. https://doi.org/10.1016/J.CLINPH.2016.03.021.

Fingelkurts Alexander A., Fingelkurts Andrew A., Bagnato S, Boccagni C, Galardi G. 2013. The value of spontaneous EEG oscillations in distinguishing patients in vegetative and minimally conscious states. In: *Suppl Clin Neurophysiol*. Vol. 62. Elsevier B.V.; p. 81–99. https://doi.org/10.1016/B978-0-7020-5307-8.00005-3

Forgacs PB, Conte MM, Fridman EA, Voss HU, Victor JD, Schiff ND. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. *Ann Neurol*. 2014:76(6):869–879. https://doi.org/10.1002/ana.24283.

Forgacs PB, Frey H-P, Velazquez A, Thompson S, Brodie D, Moitra V, Rabani L, Park S, Agarwal S, Falo MC et al. Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury

after cardiac arrest. *Ann Clin Transl Neurol*. 2017:4(2):119–129. https://doi.org/10.1002/acn3.385.

Gao R, Peterson EJ, Voytek B. Inferring synaptic excitation/inhibition balance from field potentials. *NeuroImage*. 2017:158:70–78. https://doi.org/10.1016/J.NEUROIMAGE.2017.06.078.

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. https://doi.org/10.1016/J.APMR.2004.02.033.

Giacino JT, Schnakers C, Rodriguez-Moreno D, Kalmar K, Schiff N, Hirsch J. Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? *Prog Brain Res*. 2009:177(C):33–48. https://doi.org/10.1016/S0079-6123(09)17704-X.

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. https://doi.org/10.1038/nrneurol.2013.279.

Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, Barbano R, Hammond FM, Laureys S, Ling GSF et al. Comprehensive systematic review update summary: disorders of consciousness: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology; the American congress of rehabilitation medicine. *And the Neurology*. 2018a:91(10):461–470. https://doi.org/10.1212/WNL.0000000000005928.

Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, Barbano R, Hammond FM, Laureys S, Ling GSF et al. Practice guideline update recommendations summary: disorders of consciousness. *Neurology*. 2018b:91(10):450–460. https://doi.org/10.1212/wnl.0000000000005926.

Gloor P, Ball G, Schaul N. Brain lesions that produce delta waves in the EEG. Neurology. 1977:27(4):326–333. https://doi.org/10.1212/wnl.27.4.326

He BJ, Zempel JM, Snyder AZ, Raichle ME. The temporal structures and functional significance of scale-free brain activity. *Neuron*. 2010:66(3):353–369. https://doi.org/10.1016/j.neuron.2010.04.020.

Hermann B, Stender J, Habert MO, Kas A, Denis-Valente M, Raimondo F, Pérez P, Rohaut B, Sitt JD, Naccache L. Multimodal FDG-PET and EEG assessment improves diagnosis and prognostication of disorders of consciousness. *NeuroImage Clin*. 2021:30:102601. https://doi.org/10.1016/j.nicl.2021.102601.

Hirsch LJ, Fong MWK, Leitinger M, LaRoche SM, Beniczky S, Abend NS, Lee JW, Wusthoff CJ, Hahn CD, Westover MB et al. American clinical neurophysiology Society's standardized critical care EEG terminology: 2021 version. *J Clin Neurophysiol*. 2021:38(1):1–29. https://doi.org/10.1097/WNP.0000000000000806.

Hockaday JM, Potts F, Epstein E, Bonazzi A, Schwab RS. Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. *Electroencephalogr Clin Neurophysiol*. 1965:18(6):575–586. https://doi.org/10.1016/0013-4694(65)90075-1.

Hofmeijer J, van Putten MJAM. EEG in postanoxic coma: prognostic and diagnostic value. *Clin Neurophysiol*. 2016:127(4):2047–2055. https://doi.org/10.1016/j.clinph.2016.02.002.

Hofmeijer J, Beernink TMJ, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, Putten MJAM van. 2015. Early EEG contributes to multimodal outcome prediction of postanoxic coma. *Neurology* 85(2):137–143. https://doi.org/10.1212/WNL.0000000000001742

Howell K, Grill E, Klein AM, Straube A, Bender A. Rehabilitation outcome of anoxic-ischaemic encephalopathy survivors with prolonged disorders of consciousness. *Resuscitation*. 2013:84(10):1409–1415. https://doi.org/10.1016/j.resuscitation.2013.05.015.

James G, Witten D, Hastie T, Tibshirani R. 2013. *Statistical learning*. Springer, New York, NY; p. 15–57. https://doi.org/10.1007/978-1-4614-7138-7_2

Katz DI, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1-4 year follow-up. *Prog Brain Res*. 2009:177(C):73–88. https://doi.org/10.1016/S0079-6123(09)17707-5.

Kim H, Lee UC. Criticality as a determinant of integrated information Φ in human brain networks. *Entropy*. 2019:21(10):981. https://doi.org/10.3390/e21100981.

Kondziella D, Bender A, Diserens K, van Erp W, Estraneo A, Formisano R, Laureys S, Naccache L, Ozturk S, Rohaut B et al. European academy of neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020:27(5):741–756. https://doi.org/10.1111/ene.14151.

Kustermann T, Nguepnjo Nguissi NA, Pfeiffer C, Haenggi M, Kurmann R, Zubler F, Oddo M, Rossetti AO, De Lucia M. Electroencephalography-based power spectra allow coma outcome prediction within 24 h of cardiac arrest. *Resuscitation*. 2019. https://doi.org/10.1016/J.RESUSCITATION.2019.05.021.

Laitio RM, Kaskinoro K, Särkelä MOK, Kaisti KK, Salmi E, Maksimow A, Långsjö JW, Aantaa R, Kangas K, Jääskeläinen S et al. Bispectral index, entropy, and quantitative electroencephalogram during single-agent xenon Anesthesia. *Anesthesiology*. 2008:108(1):63–70. https://doi.org/10.1097/01.anes.0000296106.52472.a6.

Lanzone J, Colombo MA, Sarasso S, Zappasodi F, Rosanova M, Massimini M, Di LV, Assenza G. EEG spectral exponent as a synthetic index for the longitudinal assessment of stroke recovery. *Clin Neurophysiol*. 2022:137:92–101. https://doi.org/10.1016/j.clinph.2022.02.022.

Lee H, Golkowski D, Jordan D, Berger S, Ilg R, Lee J, Mashour GA, Lee UC, Avidan MS, Blain-Moraes S et al. Relationship of critical dynamics, functional connectivity, and states of consciousness in large-scale human brain networks. *NeuroImage*. 2019:188:228–238. https://doi.org/10.1016/j.neuroimage.2018.12.011.

Lehembre R, Bruno MA, Vanhaudenhuyse A, Chatelle C, Cologan V, Leclercq Y, Soddu A, Macq B, Laureys S, Noirhomme Q. Resting-state EEG study of comatose patients: A connectivity and frequency analysis to find differences between vegetative and minimally conscious states. *Funct Neurol*. 2012:27(1):41–47.

Lutkenhoff ES, Nigri A, Rossi Sebastiano D, Sattin D, Visani E, Rosazza C, D'Incerti L, Bruzzone MG, Franceschetti S, Leonardi M et al. EEG power spectra and subcortical pathology in chronic disorders of consciousness. *Psychol Med*. 2022:52(8):1491–1500. https://doi.org/10.1017/S003329172000330X.

Maschke C, Duclos C, Owen AM, Jerbi K, Blain-Moraes S. Aperiodic brain activity and response to anesthesia vary in disorders of consciousness. bioRxiv.:2022 April 22.489199. 2022:10.1101/2022.04.22.489199.

Mertel I, Pavlov YG, Barner C, Müller F, Diekelmann S, Kotchoubey B. Sleep in disorders of consciousness: behavioral and polysomnographic recording. *BMC Med*. 2020:18(1):350. https://doi.org/10.1186/s12916-020-01812-6.

Millière R, Carhart-Harris RL, Roseman L, Trautwein FM, Berkovich-Ohana A. Psychedelics, meditation, and self-consciousness. *Front Psychol*. 2018:9(SEP):1475. https://doi.org/10.3389/fpsyg.2018.01475.

Miskovic V, MacDonald KJ, Rhodes LJ, Cote KA. Changes in EEG multiscale entropy and power-law frequency scaling during the human sleep cycle. *Hum Brain Mapp*. 2018. https://doi.org/10.1002/hbm.24393.

Muthukumaraswamy SD, Liley DT. 1/f electrophysiological spectra in resting and drug-induced states can be explained by the dynamics of multiple oscillatory relaxation processes. *NeuroImage*. 2018:179:582–595. https://doi.org/10.1016/J.NEUROIMAGE.2018.06.068.

Muthukumaraswamy SD, Carhart-Harris RL, Moran RJ, Brookes MJ, Williams TM, Errtizoe D, Sessa B, Papadopoulos A, Bolstridge M, Singh KD et al. Broadband cortical desynchronization underlies the human psychedelic state. *J Neurosci*. 2013:33(38):15171–15183. https://doi.org/10.1523/JNEUROSCI.2063-13.2013.

Naro A, Bramanti P, Leo A, Cacciola A, Bramanti A, Manuli A, Calabrò RS. Towards a method to differentiate chronic disorder of consciousness patients' awareness: the low-resolution brain electromagnetic tomography analysis. *J Neurol Sci*. 2016:368:178–183. https://doi.org/10.1016/J.JNS.2016.07.016.

Noirhomme Q, Brecheisen R, Lesenfants D, Antonopoulos G, Laureys S. "Look at my classifier's result": disentangling unresponsive from (minimally) conscious patients. *NeuroImage*. 2017:145:288–303. https://doi.org/10.1016/J.NEUROIMAGE.2015.12.006.

Ogilvie RD. The process of falling asleep. *Sleep Med Rev*. 2001:5(3):247–270. https://doi.org/10.1053/smrv.2001.0145.

Olesen SS, Gram M, Jackson CD, Halliday E, Sandberg TH, Drewes AM, Morgan MY. Electroencephalogram variability in patients with cirrhosis associates with the presence and severity of hepatic encephalopathy. *J Hepatol*. 2016:65(3):517–523. https://doi.org/10.1016/j.jhep.2016.05.004.

Palva S, Palva JM. Roles of brain criticality and multiscale oscillations in temporal predictions for sensorimotor processing. *Trends Neurosci*. 2018:41(10):729–743. https://doi.org/10.1016/J.TINS.2018.08.008.

Pelentritou A, Kuhlmann L, Cormack J, McGuigan S, Woods W, Muthukumaraswamy S, Liley D. Source-level cortical power changes for xenon and nitrous oxide-induced reductions in consciousness in healthy male volunteers. *Anesthesiology*. 2020:132(5):1017–1033. https://doi.org/10.1097/ALN.0000000000003169.

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. https://doi.org/10.1007/s00415-016-8196-y.

Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists. *Anesthesiology*. 2015:123(4):937–960. https://doi.org/10.1097/ALN.0000000000000841.

Rodin E, Luby E. Effects of LSD-25 on the EEG and photic evoked responses. *Arch Gen Psychiatry*. 1966:14(4):435–441. https://doi.org/10.1001/archpsyc.1966.01730100099013.

Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. *Lancet Neurol*. 2016:15(6):597–609. https://doi.org/10.1016/S1474-4422(16)00015-6.

Rossi Sebastiano D, Panzica F, Visani E, Rotondi F, Scaioli V, Leonardi M, Sattin D, D'Incerti L, Parati E, Ferini Strambi L et al. Significance of multiple neurophysiological measures in patients with chronic disorders of consciousness. *Clin Neurophysiol*. 2015:126(3):558–564. https://doi.org/10.1016/j.clinph.2014.07.004.

Russo S, Pigorini A, Mikulan E, Sarasso S, Rubino A, Zauli FM, Parmigiani S, d'Orio P, Cattani A, Francione S et al. Focal lesions induce large-scale percolation of sleep-like intracerebral activity in awake humans. *NeuroImage*. 2021:234:117964. https://doi.org/10.1016/j.neuroimage.2021.117964.

Sanchez-Vives MV, McCormick DA. Cellular and network mechanisms of rhythmic recurrent activity in neocortex. *Nat Neurosci*. 2000:3(10):1027–1034. https://doi.org/10.1038/79848.

Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. *Anesthesiology*. 2012:116(4):946–959. https://doi.org/10.1097/ALN.0b013e318249d0a7.

Sarasso S, Boly M, Napolitani M, Gosseries O, Charland-Verville V, Casarotto S, Rosanova M, Casali AG, Brichant JF, Boveroux P et al. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. *Curr Biol*. 2015:25(23):3099–3105. https://doi.org/10.1016/j.cub.2015.10.014.

Sarasso S, D'Ambrosio S, Fecchio M, Casarotto S, Viganò A, Landi C, Mattavelli G, Gosseries O, Quarenghi M, Laureys S et al. Local sleep-like cortical reactivity in the awake brain after focal injury. *Brain*. 2020:143(12):3672–3684. https://doi.org/10.1093/brain/awaa338.

Schartner MM, Carhart-Harris RL, Barrett AB, Seth AK, Muthukumaraswamy SD. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine. *LSD and psilocybin Sci Rep*. 2017:7:46421. https://doi.org/10.1038/srep46421.

Scheinin A, Kallionpää RE, Li D, Kallioinen M, Kaisti K, Långsjö J, Maksimow A, Vahlberg T, Valli K, Mashour GA et al. Differentiating drug-related and state-related effects of Dexmedetomidine and Propofol on the electroencephalogram. *Anesthesiology*. 2018:1(Xxx): 10.1097/ALN.0000000000002192.

Schiff ND. 2016. Mesocircuit mechanisms underlying recovery of consciousness following severe brain injuries: Model and predictions. In: *Brain Funct responsiveness Disord conscious*. Springer International Publishing; p. 195–204. https://doi.org/10.1007/978-3-319-21425-2_15

Scollo-Lavizzari G, Bassetti C. Prognostic value of EEG in postanoxic coma after cardiac arrest. *Eur Neurol*. 1987:26(3):161–170. https://doi.org/10.1159/000116329.

Sitt JD, King JR, El Karoui I, Rohaut B, Faugeras F, Gramfort A, Cohen L, Sigman M, Dehaene S, Naccache L. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain*. 2014:137(8):2258–2270. https://doi.org/10.1093/brain/awu141.

Snider SB, Fischer D, McKeown ME, Cohen AL, Schaper FLWVJ, Amorim E, Fox MD, Scirica B, Bevers MB, Lee JW. Regional distribution of brain injury after cardiac arrest: clinical and electrographic correlates. *Neurology*. 2022:98(12):E1238–E1247. https://doi.org/10.1212/WNL.0000000000013301.

Sokoliuk R, Cruse D. Listening for the rhythm of a conscious brain. *Brain*. 2018:141(11):3095–3097. https://doi.org/10.1093/brain/awy267.

Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. *J Clin Neurophysiol*. 1988:5(2):161–174. https://doi.org/10.1097/00004691-198804000-00003.

Tagliazucchi E. The signatures of conscious access and its phenomenology are consistent with large-scale brain communication at criticality. *Conscious Cogn*. 2017:55:136–147. https://doi.org/10.1016/j.concog.2017.08.008.

Timmermann C, Roseman L, Schartner M, Milliere R, Williams LTJ, Erritzoe D, Muthukumaraswamy S, Ashton M, Bendrioua A, Kaur O et al. Neural correlates of the DMT experience assessed with multivariate EEG. *Sci Rep*. 2019:9(1):1–13. https://doi.org/10.1038/s41598-019-51974-4.

Timofeev I. Origin of slow cortical oscillations in Deafferented cortical slabs. *Cereb Cortex*. 2000:10(12):1185–1199. https://doi.org/10.1093/cercor/10.12.1185.

Toker D, Pappas I, Lendner JD, Frohlich J, Mateos DM, Muthukumaraswamy S, Carhart-Harris R, Paff M, Vespa PM, Monti MM et al. Consciousness is supported by near-critical slow cortical electrodynamics. *Proc Natl Acad Sci U S A*. 2022:119(7). https://doi.org/10.1073/pnas.2024455119.

van Erp WS, Lavrijsen JCM, Vos PE, Bor H, Laureys S, Koopmans RTCM. The vegetative state: prevalence, misdiagnosis, and treatment limitations. *J Am Med Dir Assoc*. 2015:16(1):85.e9–85.e14. https://doi.org/10.1016/j.jamda.2014.10.014.

Vijayan S, Ching SN, Purdon PL, Brown EN, Kopell NJ. Thalamocortical mechanisms for the anteriorization of alpha rhythms during propofol-induced unconsciousness. *J Neurosci*. 2013:33(27):11070–11075. https://doi.org/10.1523/JNEUROSCI.5670-12.2013.

Vlisides PE, Bel-Bahar T, Lee UC, Li D, Kim H, Janke E, Tarnal V, Pichurko AB, McKinney AM, Kunkler BS et al. Neurophysiologic correlates of ketamine sedation and Anesthesia: A high-density electroencephalography study in healthy volunteers. *Anesthesiology*. 2017:127(1):58–69. https://doi.org/10.1097/ALN.0000000000001671.

Vogel F. The genetic basis of the normal human electroencephalogram (EEG). *Humangenetik*. 1970:10(2):91–114. https://doi.org/10.1007/BF00295509.

Wannez S, Heine L, Thonnard M, Gosseries O, Laureys S. The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol*. 2017:81(6):883–889. https://doi.org/10.1002/ana.24962.

Wutzl B, Golaszewski SM, Leibnitz K, Langthaler PB, Kunz AB, Leis S, Schwenker K, Thomschewski A, Bergmann J, Trinka E. Narrative review: quantitative EEG in disorders of consciousness. *Brain Sci*. 2021:11(6):697. https://doi.org/10.3390/brainsci11060697.

Zhou DW, Mowrey DD, Tang P, Xu Y. Percolation model of sensory transmission and loss of consciousness under general Anesthesia. *Phys Rev Lett*. 2015:115(10). https://doi.org/10.1103/PhysRevLett.115.108103.

Zilio F, Gomez-Pilar J, Cao S, Zhang J, Zang D, Qi Z, Tan J, Hiromi T, Wu X, Fogel S et al. Are intrinsic neural timescales related to sensory processing? Evidence from abnormal behavioral states. *NeuroImage*. 2021:226:117579. https://doi.org/10.1016/j.neuroimage.2020.117579.