EEG-Derived Markers to Improve Prognostic Evaluation of Disorders of Consciousness

Jlenia Toppi, Ilaria Quattrociocchi, Angela Riccio, Mariagrazia D'Ippolito, Marta Aloisi, Emma Colamarino, Floriana Pichiorri, Febo Cincotti, Rita Formisano, and Donatella Mattia

***Abstract*—Disorders of consciousness (DoC) are characterized by alteration in arousal and/or awareness commonly caused by severe brain injury. There exists a consensus on adopting advanced neuroimaging and electrophysiological procedures to improve diagnosis/prognosis of DoC patients. Currently, these procedures are prevalently applied in a research-oriented context and their translation into clinical practice is yet to come. The aim of the study consisted in the identification of measures derived from routinary electroencephalography (EEG) able to support clinicians in the prediction of DoC patients' outcome. In the present study, a routine EEG was recorded during rest from a sample of 58 DoC patients clinically diagnosed as Unresponsive Wakefulness State (UWS) and Minimally Conscious State (MCS) and followed-up for 3 months. EEG-based features characterizing brain activity in terms of spectral content and resting state networks organization were used in a predictive machine learning model to i) identify which were the most promising features in predicting patients' exit from the DoC, regardless of the clinical diagnosis and ii) verify whether such features would have been the same best discriminating UWS from MCS or specific of the outcome prediction. A predictive machine learning model was built on EEG features related to spectral content and resting state networks which returned up to 85% of performance accuracy in outcome prediction and 76% in DoC state recognition (UWS vs MCS). We provided preliminary evidence for the exploitation of a routine EEG to improve the clinical management of non-communicative patients to be confirmed in a larger DoC population.**

***Index Terms*—Disorders of Consciousness, EEG, connectivity estimation, graph theory, prognostic factors, diagnosis, machine learning.**

Received 28 November 2023; revised 24 May 2024 and 9 August 2024; accepted 12 August 2024. Date of publication 16 August 2024; date of current version 7 November 2024. This work was supported in part by the Italian Ministry of Health (MoH) through the Programme - Giovani Ricercatori 2019 under Project GR-2019-12369824, in part by the European Union's Horizon 2020 Research and Innovation Program Under the Marie Skłodowska-Curie under Grant Agreement number 778234 - DoCMA Project, and in part by the Sapienza University of Rome under Grant RM123188F229EC72 and Grant AR123188B4B7BF93. *(Rita Formisano and Donatella Mattia jointly supervised this work.) (Corresponding author: Jlenia Toppi.)*

This work involved human subjects or animals in its research. Approval of all ethical and experimental procedures and protocols was granted by Local Ethical Committee of Fondazione Santa Lucia under Application No. CE PROG. 603/2017, and performed in line with the Declaration of Helsinki.

Jlenia Toppi, Ilaria Quattrociocchi, Emma Colamarino, and Febo Cincotti are with the Department of Computer, Control and Management Engineering, Sapienza University of Rome, Via Ariosto, 25–00185 Rome, Italy, and also with the IRCCS Fondazione Santa Lucia Hospital, Via Ardeatina, 306–00179 Rome, Italy (e-mail: jlenia.toppi@uniroma1.it; ilaria.quattrociocchi@uniroma1.it; emma.colamarino@uniroma1.it; febo.cincotti@uniroma1.it).

Angela Riccio, Mariagrazia D'Ippolito, Marta Aloisi, Floriana Pichiorri, Rita Formisano, and Donatella Mattia are with the IRCCS Fondazione Santa Lucia Hospital, Via Ardeatina, 306–00179 Rome, Italy (e-mail: a.riccio@hsantalucia.it; mg.dippolito@hsantalucia.it; m.aloisi@hsantalucia.it; f.pichiorri@hsantalucia.it; r.formisano@hsantalucia.it; d.mattia@hsantalucia.it).

Digital Object Identifier 10.1109/JBHI.2024.3445118

I. Introduction

DISORDER of Consciousness (DoC) is a clinical condition characterized by alterations in arousal and/or awareness and caused by acquired brain injury [1]. DoC could be categorized in different states including coma, Unresponsive Wakefulness Syndrome (UWS), already known as Vegetative State [2], and Minimally Conscious State (MCS). Coma is a state with absence of arousal (eyes opening) and awareness (non-reflexive behaviors and command following) [3]. The UWS [4], is a condition following the acute phase of coma where the patient recovers vigilance or alertness (eyes opening) and the sleep-wake circadian cycle, but not awareness of self and surroundings [5]. The MCS has been described as a condition in which the patient recovers eye tracking ability or fluctuating command following, while remaining unable to communicate [6]. Patients can be defined as exit MCS (EMCS) when show functional object use or accurate functional communication [7].

The gold-standard to diagnose patients with DoC is the JFK Coma Recovery Scale Revised (CRS-R) which allows the clinical assessment of patients' residual visual, auditory, motor, verbal functions, patients' communication ability and arousal [8]. However, the accuracy of such clinical examination based on bedside behavioral assessment could be affected by the non-interpretable patients' behavior mainly caused by both short (seconds to hours) and long term (days to months) fluctuations in arousal [9] and/or presence of co-morbidities (spasticity, aphasia, neglect, etc.) altering their behavioral responses [10]. Accordingly, it has been estimated that approximately 40% of patients with DoC are erroneously classified as UWS [11], with evident ethical and clinical impact on patients' prognosis, treatment and end-of-life decisions. The recovery from DoC condition depends on several factors (aetiology, severity at baseline, and medical complications) [12] and also on the clinical diagnosis [13]. In fact, MCS patients compared with UWS showed more favorable prognosis in terms of consciousness and functional improvement [14]. Overcoming the critical issue of misdiagnosis in the DoC assessment would thus, make the prognostic prediction more robust to eventually assist clinicians in decisions making processes about patient care and rehabilitation [13].

Emerging evidence suggests that one way to cope with DoC clinical assessment susceptibility to biases and misdiagnosis is to look for preserved higher cognitive functions in absence of an interpretable motor behavior by measuring patients' responses directly from the brain [15]. As such, this indirect approach has been so successful that, the European Academy of Neurology has recommended the use of techniques measuring the hemodynamical or electrical brain activity in the investigation of consciousness in DoC patients as reported in the recently released guidelines on the diagnosis of coma and DoC [16].

Among the electrophysiological techniques, the electroencephalography (EEG) has been extensively utilized for DoC assessment and the several studies available summarized the performances obtained applying single categories of measures to eventually indicate how the combination of different measures would increase discriminability between VS and MCS (for a review see [17], [18], [19]). As for spectral domain, MCS patients are featured with respect to UWS for higher theta/alpha and lower delta oscillations in temporal and centro-parietal areas [20], [21], [22], as confirmed also by a direct correlation of alpha power and inverse correlation of delta content with CRS-R scores [23]. Moreover, UWS patients show more irregular, complex, and unpredictable EEG signals with respect to MCS as revealed by low level of spectral entropy, being characterized by stereotyped signals as effect of a low or absent consciousness [24], [25], [26]. As for connectivity features, MCS exhibit functional networks at rest with higher density of connections mainly located in frontal areas [27], [28], higher connection weights [29], [30], higher segregation properties [31], [32], [33] and characterized by an efficiency correlating with behavioral awareness [34].

Up to now, only few studies employed EEG-based quantitative measures during resting state condition to predict DoC patients' outcome [35], [36], [37]. Higher frequency content (lower delta and higher theta and alpha oscillations) and higher complexity (higher entropy) predict the transition from UWS to MCS or the exit from this clinical condition. Moreover, regarding connectivity analysis, higher connections' weight and density together with higher fronto-parietal communication especially in theta and alpha bands are associated to a more favorable outcome [13], [18]. Despite promising these results are still limited because of several factors such as reduced samples of patients, clinical heterogeneity, absence of a uniform criterion for the assessment of patients' outcome (different studies used different clinical scale to assess outcome), lack of a multimodal predicting model including measures belonging to different categories. For all these reasons, further investigations on a large homogeneous cohort of patients are needed to foster the translation of such research -oriented findings into reliable markers of recovery from DoC to eventually become instrumental in clinical practice.

The present study aimed at identifying informative properties in terms of spectral features and functional network organization that could be extracted from standard EEG recordings obtainable in clinical routine during five minutes of resting state (open eye) able to distinguish: i) DoC patients with positive from negative outcome and ii) UWS from MCS patients. We consecutively enrolled a sample of 58 DoC (UWS and MCS) patients who were clinically followed-up for 3 months. Advanced methodologies for EEG signal processing were used to extract features characterizing the electrical brain activity in terms of spectral content and resting state networks organization (global properties, communication between hemispheres and antero-posterior areas). Two different predictive machine learning models which included both spectral and connectivity features, were generated to i) identify which were the most promising features in predicting patients' exit from the disorder of consciousness regardless of the clinical diagnosis (UWS or MCS) and ii) verify whether such features would have been overlapped to those best discriminating UWS from MCS or specific of the outcome prediction. As such, this approach was adopted to enable the estimation of predictive features not directly dependent on the clinical diagnosis thus, limiting its possible confounding effect (i.e., clinical misdiagnosis).

II. Methods

A. Subjects

A total of 58 patients (29males/29females, mean age: 45±16 yr, CRS-R score: 11±5) diagnosed as DoC following a severe acquired brain injury (i.e., Glasgow Coma Scale [38] $\leq$ 8 in the acute phase) were enrolled for the study. CRS-R [39] was used to diagnose 18 patients as UWS (10males/8females, mean age: 40±15 yr, CRS-R score: 5±2) and 40 patients as MCS (19males/21females, mean age: 47±16 yr, CRS-R score: 14±3). Clinical and demographic characteristics of patients are summarized in Table I.

The CRS-R was administered also prior to the EEG recording session to confirm the diagnosis. No changes in the drugs with effects on the central nervous system were performed within the last 2 weeks preceding the EEG recordings. All patients were clinically followed up at 3 months from the neurophysiological recording (timepoint: T_1) using the same clinical scales of T_0. The present study protocol was approved by the local (Fondazione Santa Lucia) Ethics committee (CE PROG. 603/2017) and conducted in accordance with the standards of the 2013 Declaration of Helsinki. Written informed consent was obtained by the patient's legal surrogates.

B. EEG Recordings

Scalp EEG potentials were acquired by means of 19 sintered Ag/AgCl electrodes (SD plus amplifier, Micromed, Italy) arranged according to 10-20 International System (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, 01, 02; Fpz and Oz as reference and ground respectively; 250 Hz sampling frequency). Recordings were obtained at resting state (open eyes) for 5' during a routine EEG recording. An expert EEG

TABLE I
DEMOGRAPHICAL AND CLINICAL CHARACTERISTICS OF THE PATIENTS ENROLLED IN THE STUDY

	N	*AGE** *(yr)*	*GENDER*	*ETIOLOGY*	*Temporal Criteria*	*CRS-R** *score*	*OUT-COME 3M FUP*
DoC	*58*	*45(±16)*	*29F/29M*	*22T/6AN/27V/3OT*	*2A/34P/22C*	*11(±5)*	*28O+/30O-*
UWS	*18*	*40(±15)*	*8F/10M*	*9T/4AN/4V/1OT*	*11P/7C*	*5(±2)*	*2O+/16O-*
MCS	*40*	*47(±16)*	*21F/19M*	*13T/2AN/23V/2OT*	*2A/23P/15C*	*14(±3)*	*26O+/14O-*

List of acronyms: A – acute (DoC present for less than 28 days), AN - anoxic, C – chronic (DoC after 3 months in non-traumatic and after 12 months in traumatic cases), F – female, M – male, O+ - positive outcome at 3 months follow-up, O- - negative outcome at 3 months follow-up, OT – other; P – prolonged (DoC after at least 28 days from the brain injury), T – traumatic, V – vascular. * mean (±standard deviation).

technician was instructed to monitor for potential occurrence of sleep during the recording.

C. Pre-Processing

Raw EEG signals were band-pass filtered (1–20 Hz) to block direct current and to exclude the frequency range typical of muscular artifacts, commonly occurring in this category of patients. Independent Component Analysis (ICA) was used to remove ocular artefacts only when recognizable vertical eye-movements were present. Signals were then segmented into epochs of 1 sec duration; trials with at least one channel with an amplitude exceeding in absolute value the threshold of 100 μV were excluded from the analysis (rejection rate of around 11% for UWS and 6.5% for MCS). A total of 100 trials were randomly extracted from the 5' data set for each patient to allow the subsequent analyses on the same amount of individual data. Pre-processing was computed by means of Brain Vision Analyzer 2.0 (Brain Products GmbH, Germany) and Matlab R2021b (The MathWorks, Inc.).

D. Spectral Analysis

Power Spectral Density (PSD) was computed by means of Welch periodogram on pre-processed EEG data related to the midline electrodes (Fz, Cz, Pz). In particular, we considered as epochs of the periodogram the 1s trials obtained by segmenting the entire EEG resting state trace of 5 minutes with no overlap (see Pre-processing paragraph above). Each trial was tapered by means of Hann window and then transformed in the frequency domain by means of Fast Fourier Transform, considering a spectral resolution equal to 0.25 Hz. The Welch's estimate of PSD was computed by averaging the modified periodograms obtained across the different epochs. Five out of 58 patients were excluded from spectral analysis due to the presence of out-of-range PSD values in beta band highly attributable to a residual muscular component which could be interpreted erroneously as fast brain oscillations related to high cognitive processing.

In order to objectively quantify spectral properties of EEG signals at rest we defined two categories of spectral indices characterizing the magnitude and the frequency distribution of the spectrum (see Table II). Magnitude indices measured the relative contribution of a specific band to the global power and consisted in the relative power spectrum for the following bands: delta [1], [2], [3], [4] Hz, theta (4–7] Hz and alpha (7–12] Hz, with a frequency resolution of 0.25 Hz. Frequency indices described the frequency distribution of the spectrum giving information on the central frequencies of the spectrum and its extension and included: Peak Power Frequency (PPF), Median Frequency (MF), Spectral Edge Frequency (SEF), Main Dominant Frequency (MDF) [40]. Each index was computed for the 3 midline channels (Fz, Cz, Pz) by means of Matlab R2021b (The MathWorks, Inc.) for each patient included, as representative of frontal central and parietal brain areas. Indeed, no different results in the spectral properties were found between i) F3, Fz and F4, ii) C3, Cz and C4, iii) P3, Pz and P4.

E. Connectivity Analysis

Functional resting state networks were estimated applying Partial Directed Coherence (PDC) to pre-processed EEG data acquired from 19 electrodes. PDC is a multivariate spectral connectivity estimator that determines the directed influences between any given pair of signals in a multivariate dataset [41]. In particular, EEG data cleaned and segmented as reported in pre-processing section were fed into a multivariate autoregressive model used as linear predictor. The MVAR parameters were estimated by minimizing the prediction error of the model and then transformed in frequency domain and normalized across the rows of the parameters' matrix, in order to obtain a PDC weight for each pair of electrodes, direction and frequency. Such PDC values were then averaged in three frequency bands: delta [1–4) Hz, theta [4–8) Hz and alpha [8], [9], [10], [11], [12] Hz with a frequency resolution equal to 1 Hz. The average was repeated for each pair of electrodes and each direction. The obtained connectivity matrices were statistically validated against null-case by means of the asymptotic statistics, a theoretical approach based on the assumption that PDC estimator tends to a χ^2 distribution in the null case (i.e., lack of connection) and to a gaussian distribution in the non-null case (i.e., existing connection). Therefore, the statistical threshold of significance corresponds to the 95th percentile of the χ^2 distribution obtained from data applying Monte Carlo method. The statistical validation is repeated by defining a specific statistical threshold of significance for each frequency band, each connection and each direction [31], [42]. The statistical assessment allowed to discard existing from non-existing connections in each pattern and was used to transform each connectivity matrix in an adjacency matrix as input for the graph theory computation. This approach

TABLE II
SPECTRAL AND CONNECTIVITY INDICES USED

Spectral Indices		*Connectivity Indices*		
Magnitude Indices	*Frequency Indices*	*Global Indices*	*Hemispheres relationships*	*Anterior-posterior communication*
Delta Relative Power (RPδ)	*Peak power frequency (PPF)*	*Global Efficiency (GE)*	*L connections*	*A connections*
Theta Relative Power (RPθ)	*Mean frequency (MF)*	*Local Efficiency (LE)*	*R connections*	*P connections*
Alpha Relative Power (RPα)	*Median frequency (MDF)*	*Path Length (PL)*	*Inter-hemispheric connections (IHC)*	*AP connections*
	Spectral edge frequency (SEF)	*Clustering coefficient (CC)*	*LR influence*	*AP influence*
		Small-Worldness (SW)	*LR asymmetry*	*AP asymmetry*
				APL connections
				APR connections

List of spectral and connectivity indices used to characterize resting state EEG in doc patients. List of acronyms: A - anterior, AP - anterior-posterior, APR – anterior-posterior right, APL – anterior-posterior left, L – left, LR – left-right, P – posterior, R – right.

has been demonstrated to contribute to a higher reliability of the indices computed to characterize the main properties of the network [43].

To compute indices describing the main local and global properties of the investigated patterns, we adopted measures derived from a graph theoretical approach computed on adjacency matrices as described above [44]. In particular, we considered indices belonging to three different categories (Table II): i) global indices describing integration and segregation properties of the network, ii) indices describing relationship between hemispheres and iii) indices describing relationship between anterior and posterior regions (also separately for the two hemispheres). As for global indices we included *characteristic path length* and *global efficiency* for measuring integration properties while *local efficiency* and *clustering coefficient* were used to investigate segregation properties. Then to summarize integration and segregation characteristics, *small-worldness* index was computed [45], [44], [46]. As for the other two categories we defined: i) indices specifically measuring the *density of connections within* particular regions of the network; ii) *asymmetry* quantifying the balance of connections within two different communities of the network; iii) index measuring *density of connections between* two different regions of the network and iv) influence investigating the existence of dominant direction of communication between two communities. All these indices were computed within and between specific communities in the network: left (L) and right (R) hemispheres and anterior (A) and posterior (P) regions. The mathematical formulation for such indices was adapted from [31] and reported in the appendix. Each index was calculated for all the subjects included in the analysis and for the 3 frequency bands. Connectivity analysis included 54 patients: 4 out of 58 patients were excluded from this analysis since the estimated functional networks were too sparse (density inferior to 10%) to allow the extraction of accurate and reliable measures describing their properties. The analysis was computed by means of Matlab R2021b (The MathWorks, Inc.).

F. Statistical Analysis 1: EEG-based Indices Predicting DoC Patients' Outcome

We first conducted an analysis investigating the potential of resting state spectral and connectivity indices to predict the outcome of DoC patients irrespective of the original diagnosis at study entry (UWS or MCS). The analysis was performed using neurophysiological data acquired at T_0 and the patients' outcome as stated by the clinical assessment at T_1. According to the CRS-R scores obtained at T_1, patients were divided in two groups: positive (O+) and negative outcome (O-). O+ group included patients who exited the disorder and were diagnosed as EMCS by CRS-R at T_1. O- included patients who either died or did not change their clinical status or changed their status from UWS to MCS diagnosis or vice versa without exiting from the DoC. O+ group included 28 patients (12males/16females, mean age: 47,32±17,71yr) and O- group 30 (17males/13females, mean age: 42,1±14,17yr). No significant differences were found between O+ and O- groups in terms of age (unpaired t-test, p-value = 0,2187) and gender (χ-squared test, p-value = 0,2932).

We statistically compared spectral and connectivity indices obtained in O+ and O- patients to describe differences in terms of EEG characteristics between such two categories of patients, after checking for data normality (Lilliefors test, alpha equal to 0.05). Indices satisfying the normality hypothesis were compared between O+ and O- by means of unpaired t-test (significance level equal to 0.05, False Discovery Rate correction for multiple comparisons), while non-normal distributions were compared by means of Wilcoxon rank test (alpha equal to 0.05). Such statistical tests were used as a feature selection step of the classification approach described below. The aim was to identify which are the features that discriminate the two classes under study, and to use this information not to maximize the discriminative power of the classifier, but to reduce the number of combinations of features to be tested considering only the features more representative of the neurophysiological phenomena under examination.

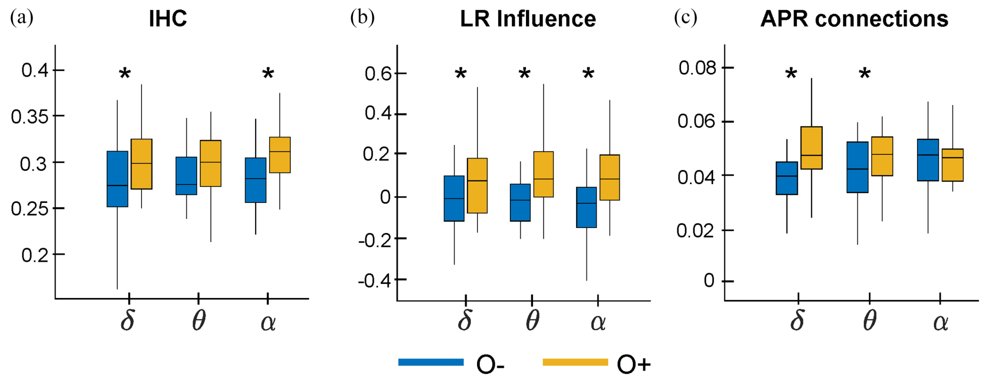

Fig. 1. Box plot reporting results of the comparison between connectivity indices extracted for negative (in blue) and positive (in yellow) outcome. The indices considered are as follows: IHC (panel (a), LR influence (panel (b), and APR connections (panel (c) all in delta, theta and alpha bands. The symbol $*$ indicates statistically significant difference between VS/UWS and MCS (independent samples t-test, alpha equal to 0.05).

A machine learning model was built by means of a leave-one-subject-out approach to identify which spectral and connectivity indices have predictive value for patients' outcome. A Supported Vector Machines (SVM) classifier with linear kernel was trained using data belonging to the entire set of patients except for one patient who was used to test the classifier built on the other subjects. Features space included triplets of indices resulted as statistically significant in the t-test computed between O+ and O- groups and thus had dimension equal to $(Nsub - 1)\ x3$. The analysis was repeated leaving out one patient each time, for all the patients included and the related classification accuracy (number of correctly classified patients over the total) was evaluated.

G. Statistical Analysis 2: EEG-based Indices Discriminating UWS From MCS

We conducted an analysis identifying resting state spectral and connectivity indices able to discriminate UWS from MCS patients to verify if such indices are overlapped or not to those resulted as predictive of the patients' outcome. The analysis was performed considering the clinical and neurophysiological data at T_0. According to CRS-R diagnosis, 40 out of 58 patients were assessed as MCS (19males/21females, mean age: 46,85 $\pm$ 16,03yr), 18 as UWS (10males/8females, mean age: 39,67 $\pm$ 15,38yr).

No significant differences were found between the two groups both in terms of age (unpaired t-test, p-value = 0,1157) and gender (χ-squared test, p-value = 0,5702).

We statistically compared spectral and connectivity indices obtained in UWS and MCS patients to describe differences in terms of EEG characteristics between such two categories of patients, after checking for data normality (Lilliefors test, alpha equal to 0.05). We applied unpaired t-test (significance level equal to 0.05, False Discovery Rate correction for multiple comparisons) for all the indices satisfying the normality hypothesis, while non-normal distributions were compared by means of Wilcoxon rank test (alpha equal to 0.05). A leave-one-subject-out approach was used on datasets composed by triplets of features, one for each category of indices resulted as statistically different between UWS and MCS.

III. Results

A. EEG-Based Indices to Discriminate Positive From Negative DoC Patients' Outcome At Three-Months Follow-Up

The statistical comparison between O+ and O- patients revealed that only 2 categories of indices were significantly different between groups. These were indices descriptive of either hemispheres' relationship and communication between anterior and posterior regions. As for hemispheres relationship, we found that patients with positive outcome (O+) showed a significantly higher number of inter-hemispheric connections in delta ($p = 0.0416$) and alpha ($p = 0.0132$) bands (Fig. 1, panel a) that were mainly directed from left to right hemisphere in all analyzed frequency bands (Fig. 1, panel b) with respect to those with negative outcome (O-). In fact, LR influence was significantly different between O+ and O- in delta ($p = 0.0239$), theta ($p = 0.0092$) and alpha (*0.0013*) bands. The O+ patients also showed significantly higher indices of communication between anterior and posterior areas in the right hemisphere both in delta ($p = 0.0052$) and theta ($p = 0.0314$) bands (Fig. 1, panel c).

The significant features described above were used in triplets to train a classifier discriminating positive from negative outcome in DoC patients. The classification accuracy obtained for all the combinations is reported in Fig. 2(a).

The model with the highest discrimination accuracy (85%) was built using as features the following indices: LR influence in alpha, APR connections in delta, IHC in delta. The related features space is reported in Fig. 2(b) where it can be noted how the two classes O+ and O− are highly separable by a plane.

B. EEG-based Indices to Discriminate UWS From MCS Patients

As for spectral indices, we found significant differences between UWS and MCS in 3 magnitude (RPδ, RPθ, RPα) and 2

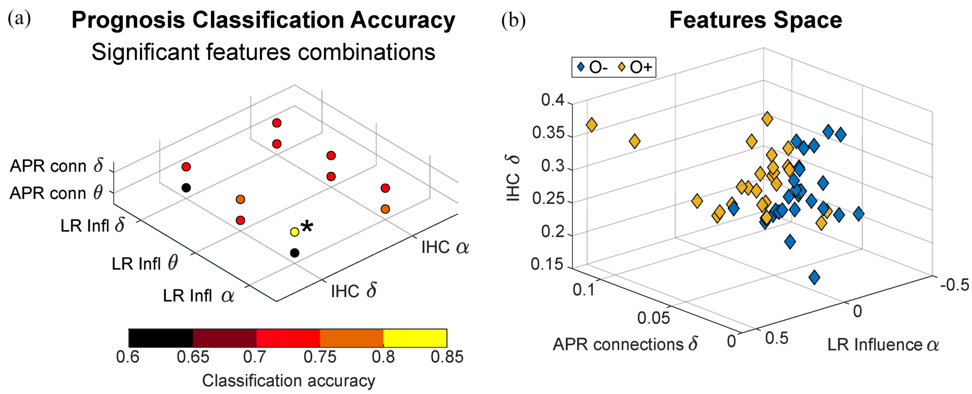

Fig. 2. (a) Results of the leave-one-subject-out classification approach discriminating DoC patients with positive from negative outcome. Each point in the three-dimensional space represents the value of classification accuracy (coded by means of the hot colormap) obtained for each tested triplet of features filtered by the statistical analysis: on x-axis LR influence in delta, theta and alpha bands, on y-axis IHC in delta and alpha bands, on z-axis APR connections in delta and theta bands. The symbol $*$ highlights the features triplet giving the highest classification accuracy. (b) features space related to the highest classification accuracy (in yellow in panel (a) obtained using as features the following indices: IHC in delta, APR connections in delta and LR influence in alpha.

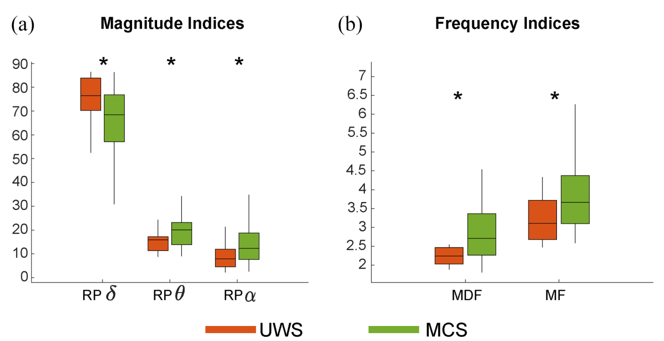

Fig. 3. Box plot reporting the distributions of spectral indices obtained for UWS (in orange) and MCS patients (in green) at Pz location. The indices considered are as follows: relative power (RP) in delta, theta and alpha bands (panel (a), median (MDF) and mean (MF) frequencies (panel (b). The symbol $*$ indicates statistically significant difference between UWS and MCS groups (independent samples t-test, alpha equal to 0.05).

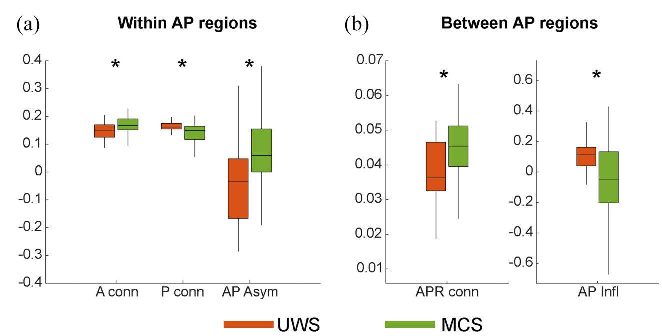

Fig. 4. Box plot reporting distributions of indices measuring the relationship between anterior and posterior areas extracted for UWS (in orange) and MCS (in green) in delta band. The indices considered are as follows: anterior connections (A connections), posterior connections (P connections) and anterior-posterior asymmetry (AP asymmetry) (panel a, connections within areas), anterior-posterior connections in right hemisphere (APR connections) and anterior-posterior influence (AP influence) (panel b, connections between areas). The symbol $*$ indicates statistically significant difference between UWS and MCS groups (independent samples t-test, alpha equal to 0.05).

frequency (MF and MDF) indices computed for Pz electrodes (Fig. 3).

In particular, relative powers showed a significant higher spectral content in delta ($p = 0.012$) band whereas a lower contribution of theta ($p = 0.0337$) and alpha (0.0237) oscillations was observed in UWS with respect to MCS patients (panel a, Fig. 3). Similarly, we found that MDF ($p = 0.009$) and MF ($p = 0.0209$) indices were significantly lower in UWS with respect to MCS (panel b, Fig. 3). Similar results were obtained for Fz electrode.

As for connectivity measures, significant differences between UWS and MCS were found only for the measures describing the communication between anterior and posterior areas only in delta band. No between-group significant differences were found in inter-hemispheric communication in all frequency bands. The Fig. 4 illustrates the between-group distributions obtained for the indices measuring the relationship between anterior and posterior areas in delta band.

It is noteworthy how the organization of the communication within and between anterior and posterior areas of the brain can be a sign of the 2 different clinical conditions. The MCS group is characterized by a higher density of connections within the anterior areas (A connections, $p = 0.0156$) and by a lower density of connections within the posterior regions (P connections, $p = 0.0085$) with respect to UWS in delta band. These results were confirmed by anterior-posterior asymmetry index which was higher ($p = 0.0037$) and positive (prevalence of anterior over posterior) in MCS with respect to UWS in delta band (Fig. 4, panel a). As for the communication between areas, the anterior-posterior communication was significantly higher in MCS with respect to UWS especially in the right hemisphere (APR connections, $p = 0.0057$) (Fig. 4, panel b). Finally, we found a prevalence of connections going from anterior to posterior areas (AP influence, $p = 0.0054$) in UWS (AP influence

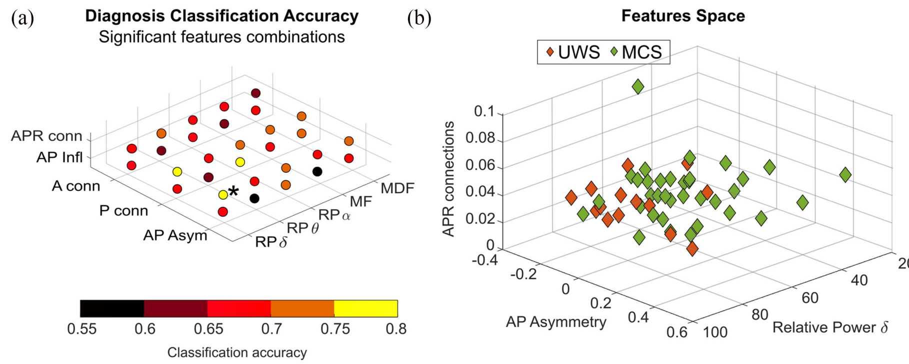

Fig. 5. (a) Results of the leave-one-subject-out classification approach discriminating UWS from MCS patients. Each point in the three-dimensional space represents the value of classification accuracy (coded by means of the hot colormap) obtained for each of the tested triplet of features: on x-axis global connectivity indices (LE, Cl, SW), on y-axis spectral indices in Pz (MDF, MF, RPδ, RPθ, RPα), on z-axis connectivity indices measuring interaction between anterior-posterior areas of the scalp (A connections, P connections, AP asymmetry, AP influence, APR connections). The symbol $*$ highlights the features triplet giving the highest classification accuracy. (b) features space related to the highest classification accuracy (in yellow in panel (a) obtained using as features the following indices: APR connections in delta, LE in delta and MDF at Pz.

positive) while in MCS the flux between the two regions is symmetrically bidirectional (AP influence almost around 0). The indices resulted as significant in the between group comparison (UWS versus MCS) were used as features to train the classifier aimed at discriminating UWS from MCS patients. All the possible triplets of features were tested extracting each feature from one of the three aforementioned categories: spectral indices and within and between anterior and posterior areas communication indices. Classification accuracy obtained for all the combinations is reported in Fig. 5, panel a. The best performance of 76% was obtained for three different triplets including i) RPδ in Pz, APR connection and AP asymmetry in delta band (see Fig. 5(b) for the corresponding feature space), ii) RPδ in Pz, APR connection and P connections and iii) RPα in Pz, AP influence and P connections. It is noteworthy how the presence of APR connections index in the triplet returns the highest performance independently from the combination with the other two categories of indices.

IV. Discussion

In the present study, we isolated EEG-based measures able to predict the outcome of patients fulfilling the clinical criteria for a diagnosis of UWS or MCS. Such measures were extracted from standard EEG recordings which were routinely executed during clinical practice, and they predicted the positive outcome (i.e., evolving from UWS or MCS into EMCS) with up to 85% of accuracy. Bearing in mind that these findings need to be consolidated on a large (possibly multicentric) cohort of DoC patients, they provide evidence for the exploitation of a routine EEG recording to substantially improve the diagnosis and prognosis of non-communicative patients. We found that our sample of DoC patients with positive outcome at 3-month follow-up showed significantly higher magnitude of mainly right antero-posterior connections estimated in the EEG low frequency oscillations, (Fig. 1(c)). Similar connectivity pattern was also found between MCS and UWS in favor of MCS (Fig. 4(b)).

These findings are in line with previous studies conducted with high density EEG technique which requires a substantial higher number of electrodes than that used in clinical routine as in our study [47], [48]. These studies provided evidence that the level of fronto-parietal communication positively correlates with the level of consciousness [47] and can predict a clinical change from UWS to MCS [48] or a long-term (1 year) positive outcome [47]. Our finding of a right hemisphere lateralization of the significantly higher magnitude of the fronto-parietal connectivity in O+ patients is novel with respect to the currently available EEG studies. Previous evidence emerging from functional Magnetic Resonance Imaging (fMRI) technique have indicated how the so-called Default Mode Network (DMN), a resting state network including posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) and bilateral parietal cortex (LPC) is highly modulated by the level of consciousness [49]. In particular, UWS patients have been described to retain only the activation of PCC within the DMN whereas MCS show a general decrease of DMN connectivity preserving the involvement of the prefrontal and parietal areas with a specific right lateralization with respect to healthy controls [50].

The limited spatial resolution of the EEG technique only allows us to speculate that the observed increase of EEG-derived lateralized fronto-parietal connectivity which not only identifies the patients' category (UWS or MCS) and indirectly the level of consciousness but also their positive outcome, could reflect the functional neuroimaging changes in the DMN.

Our EEG findings also indicate that a significant higher number of IHC with left to right hemisphere direction estimated in delta, theta and alpha bands characterized patients with positive with respect to those with a negative outcome regardless the initial diagnosis of UWS and MCS (Fig. 1(a) and (b)). As such this is a novelty with respect to previous EEG-based studies investigating potential markers to predict outcome in DoC [17], [18]. On the other hand, several fMRI studies reported a reduction of inter-hemispheric connectivity in DoC patients with respect to healthy control and its correlation with the level of consciousness [51], [52]. In our case, the higher hemispherical inter-connection in O+ patients might be interpreted as specifically related to outcome that is a sign of recovery.

Altogether our findings allow us to speculate that a more favorable outcome would be associated to a higher level of integration between the different brain areas as indicated by the observation of more functional connections linking the left and right hemispheres as well as frontal and parietal areas in our sample of O+ patients.

This is in line with two previous EEG studies reported that the overall number of connections within a resting state network together with its total weight can be interpreted as relevant signs for a more positive outcome in DoC [33], [53].

The value of our findings obtained from routinely performed EEG recordings was also corroborated by the output of the outcome predictive model which was built upon the connectivity indices commented in the above. The combination of indices measuring the magnitude of the IHC, the LR influence and the right fronto-parietal communication allowed to discriminate positive and negative outcome of patients with an accuracy of 85% (Fig. 2). To the best of our knowledge, this is the first EEG study in which a predictive model for DoC patients' outcome was built including multivariate (EEG-based) measures, each of which describing a specific aspect of the brain electrical activity of DoC patients but collectively accounting for up to 85% of outcome prediction. However, such results should be confirmed by studies involving a larger population of patients.

Only two previous studies in DoC employed a classification approach to predict outcome based on EEG-derived indices [33], [47] using one single feature (coherence in theta or fronto-parietal connections in delta) with the resulting performance of 76%–78% (AUC). We are aware that caution should be taken when performing a direct comparison between our results and others available in the literature since many factors (number of patients, machine learning approach, classifier type, metrics used to assess patients' outcome, performance parameter, etc …) could affect the data analysis thus preventing from an unbiased conclusion to be drawn.

As for the spectral indices computed in our population of UWS and MCS patients we found a slowing of the EEG oscillations in UWS with respect to MCS as testified by a higher delta power, lower theta and alpha power and lower median and mean frequency over the frontal and parietal areas (Fig. 3(a) and (b)). Previous EEG studies reported that delta power is significantly higher in UWS than in MCS patients while theta and alpha power show the opposite tendency [54], [55], [56]. Power ratio between slow and high frequency activity is higher in UWS patients than in MCS [18] and this EEG slowing is reflected also in the median and mean PSD frequency [30].

The alpha oscillations were demonstrated to have a key role in discriminating and predicting levels of consciousness since the presence of a dominant posterior alpha background and the absolute alpha power are specific feature of MCS [17]. All in all, the EEG spectral features of our sample of DoC patients are in line with the already available evidence of their role in characterizing UWS and MCS condition.

When considering the clinical diagnosis in our sample of DoC patients, we found that MCS condition was characterized by a higher number of connections in the frontal areas and a lower number of connections in the posterior areas (confirmed by the AP asymmetry) with respect to UWS. Moreover, the MCS group of patients showed right AP connection index significantly higher than UWS patients. This finding is consistent with what we observed in terms of outcome prediction; indeed, the magnitude of AP connections over the right hemisphere was crucial in determining a positive outcome. Overall, these findings have never been described in previous EEG studies. Although with caution, due to the small and imbalanced sample size, we might interpret these findings in light of what has been found in fMRI domain about the loss of the mPFC activation within the DMN observed in UWS patients [50].

Our model to discriminate MCS from UWS returned best performance (76% accuracy) with relative power in delta band at Pz, AP asymmetry and APR indices were used as features. In other words, the EEG frequency oscillations and the communication within and between frontal and parietal areas appear to be crucial factors in our case to discriminate the consciousness level. Although with caution due to the small number of patients included and imbalanced in terms of observations in UWS and MCS groups, we observe that the accuracies are comparable [47] or even better [33] than those obtained in previous EEG studies.

We are aware that the current study has a main limitation in the patients' sample size with an unbalanced categorization between UWS and MCS thus, the obtained results should be confirmed in a larger population of DoC and validated on an external population different from the one used in this study (external validation for outcome prediction). Nevertheless, our study indicates that EEG recordings routinely performed in clinical practice can be exploited to isolate measures which could allow improving assessment also in terms of outcome of extremely complex clinical condition such as DoC. However, future studies using multimodal assessment with high-density EEG and functional MRI should confirm the main findings of this work with a higher spatial resolution, which was sacrificed here for ease of integration into clinical routine.

In addition, another limitation of the study is the fact that all the results obtained and reported in the current manuscript were obtained from a single EEG screening session. However, it has recently been demonstrated how the behavioral fluctuations reported in this category of patients, especially in MCS patients, are also associated with and described by daily fluctuations in EEG-based features [54]. Future work should address such aspects by demonstrating the robustness of the approach proposed in this manuscript between several repetitions of the EEG screening during the day. The results of both diagnostic and prognostic classifiers should therefore be treated with caution, as the EEG signals recorded from MCS patients, which are taken once a day, may depend on the specific time of sampling and may not be indicative of the general state of the patient, due to the well-known fluctuations in their brain states.

Another important aspect to consider in the interpretation of the results obtained is the correlation between the time series included in the MVAR model as a consequence of volume conduction when the PDC estimation is computed from signals recorded from the scalp [57], [58]. To mitigate such an issue, other connectivity estimators known to be less affected by this phenomenon could be used. However, their robustness to the volume conduction is at the expense of spurious connections within the network due to cascade or indirect effects typical of bivariate approaches or noise sensitivity as demonstrated for non-linear estimators. As an alternative to changing the estimator, spatial filters could be applied to separate sources or remove inter-electrode correlation, bearing in mind that their action may also mask or alter connectivity between different brain regions. Both of these options are less feasible for clinical applications as the effect of the lesion is not easy to predict. To mitigate this phenomenon, but keeping an estimator that has been shown to be reliable and accurate in different clinical applications [31], [59], we compared networks between different conditions with the same electrode configuration (i.e., same montage, same reference) and eliminated the effect of spurious connections induced by volume conduction. In fact, VS/UWS and MCS patients or O+ and O- patients in our study were all screened by using the same EEG montage and reference. It is therefore reasonable to assume that the significant differences between network structures found in the paper are not related to such an effect, which is common to all subjects. Future work should address the problem of the dependence of the network structure and its properties on the estimator used to obtain the connectivity matrix. An interesting work should search for properties eventually invariant to the estimator used or should identify the most reliable estimator in order to remove all the confoundings introduced by the mathematical approach used, and thus allow an effective characterization of the network.

The final limitation relates to the method used to select features and the construction of predictive models. We adopted a filtering approach to feature selection, which ensures that the features that best fit the regressor (target vector) are found, rather than using a wrapper method that searches for well-performing subsets of features whose interpretability would be disconnected from physiology. Thus, we applied a simple univariate feature selection approach, based on statistical tests, only to identify which are the features that discriminate the two classes under study, and to use this information not to maximise the discriminative power of the classifier, but to reduce the number of combinations of features to be tested, considering only those features that are more representative of the neurophysiological phenomena under study. Once we have filtered the features on the basis of such a univariate approach, we grouped them into triplets in order to map the different domains of characterization of the brain networks and provided them as input to the classifier. We tested all possible combinations, keeping the rule about the domains (one index for each domain). This allowed us to answer our initial question: what are the differences in resting-state network properties between two different levels of DoC or between a good and a bad prognosis? When a large and balanced sample of patients will be available, more sophisticated approaches to feature selection and classification, including machine learning and deep learning, will be used to translate these initial results into a tool to assist clinicians in making medical decisions, both in terms of diagnosis and prognosis. In addition, unsupervised approaches should be used to assess any discordance between the clinical diagnosis and the results of the computational approaches based on EEG-derived indices as markers of misdiagnosis.

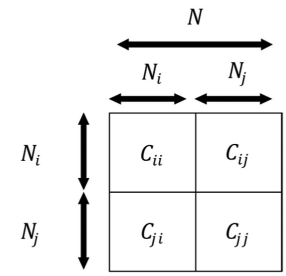

Fig. 6. Schematic representation of a generic adjacency matrix where two different communities are clearly identified.

In conclusion, the employment of advanced methodologies for EEG signal processing allowed to identify EEG-based features, mapped in spectral and connectivity domains, mostly related to a favorable outcome, and best discriminating UWS from MCS patients. Future works should assess the replicability of our results in a larger DoC population and validate the predictive models built in the present work on an external population of patients in order to demonstrate their robustness and generalizability and thus open to their employment in the clinical routine settings.

Appendix

Let's consider a generic connectivity network mathematically described by its corresponding adjacency matrix (Fig. 6), naming the two regions as R_i and R_j, constituted by N_i and N_j number of nodes respectively, graph theory allows to define intra-region and inter-regions communities. Intra-region communities describe the communication of nodes within the region and are located across the main diagonal of the adjacency matrix (C_{ii} for region R_i and C_{jj} for region R_j).

Inter-regions communities describe the communication between different regions of the network and are located outside the main diagonal of the matrix (C_{ij} , C_{ji} inter-regions community associated to region R_i and R_j from i to j and from j to i, respectively).

Given the network's structure of Fig. 6, it is possible to define four indices.

Connection density within region i: Fraction of the connections of the network existing within the community C_{ii}, defined as

$$CD_{ii}^{W} = \frac{con_{C_{ii}}}{con_{TOT}} \tag{1}$$

where $con_{C_{ii}}$ is the number of connections within the community C_{ii} and con_{TOT} represents the total number of connections existing in the network.

Asymmetry. Difference of fractions of all the possible connections existing within the communities C_{ii} and C_{jj}, defined as

$$A = \frac{con_{C_{ii}}}{N_i\,(N_i - 1)} - \frac{con_{C_{jj}}}{N_j\,(N_j - 1)} \tag{2}$$

Where $con_{C_{ii}}$ is the number of connections within C_{ii}, $con_{C_{jj}}$ is the number of connections within C_{jj}, $N_i(N_i-1)$ is the number of all the possible connections within C_{ii} and $N_j(N_j-1)$ is the number of all the possible connections within C_{jj}.

Connection density between regions i and j: Fraction of the connections of the network existing between the communities C_{ii} and C_{jj}, defined as

$$CD_{ij}^{B} = \frac{con_{C_{ij}} + con_{C_{ji}}}{con_{TOT}} \tag{3}$$

Where $con_{C_{ij}}$ is the number of connections from community C_{ii} to C_{jj}, $con_{C_{ji}}$ is the number of connections from community C_{jj} to C_{ii}, con_{TOT} is the number of connections existing in the network.

Influence: Difference of fractions of connections directed from C_{ii} to C_{jj} and connections directed from C_{jj} to C_{ii}, defined as

$$Inf = \frac{con_{C_{ij}} - con_{C_{ji}}}{N_i N_j} \tag{4}$$

where $con_{C_{ij}}$ is the number of connections from community C_{ii} to C_{jj}, $con_{C_{ji}}$ is the number of connections from community C_{jj} to C_{ii}, and $N_i N_j$ is the number of all possible connections between C_{ii} and C_{jj}.

References

[1] A. M. Owen, "Disorders of consciousness," *Ann. New York Acad. Sci.*, vol. 1124, no. 1, pp. 225–238, 2008, doi: 10.1196/annals.1440.013.

[2] B. Jennett and F. Plum, "Persistent vegetative state after brain damage. A syndrome in search of a name," *Lancet*, vol. 299, no. 7753, pp. 734–737, Apr. 1972, doi: 10.1016/s0140-6736(72)90242-5.

[3] J. B. Posner, C. B. Saper, N. Schiff, and J. Claassen, *Plum and Posner's Diagnosis and Treatment of Stupor and Coma*, 5th ed. Oxford, U.K.: Oxford Univ. Press, 2019.

[4] S. Laureys et al., "Unresponsive wakefulness syndrome: A new name for the vegetative state or apallic syndrome," *BMC Med.*, vol. 8, 2010, Art. no. 68, doi: 10.1186/1741-7015-8-68.

[5] S. Ashwal, "Medical aspects of the persistent vegetative state (1). The multi-society task force on PVS," *New England J. Med.*, vol. 330, no. 21, pp. 1499–1508, May 1994, doi: 10.1056/NEJM199405263302107.

[6] J. T. Giacino et al., "The minimally conscious state: Definition and diagnostic criteria," *Neurology*, vol. 58, no. 3, pp. 349–353, Feb. 2002.

[7] Y. Sun et al., "Personalized objects can optimize the diagnosis of EMCS in the assessment of functional object use in the CRS-R: A double blind, randomized clinical trial," *BMC Neurol.*, vol. 18, no. 1, Apr. 2018, Art. no. 38, doi: 10.1186/s12883-018-1040-5.

[8] J. T. Giacino, K. Kalmar, and J. Whyte, "The JFK coma recovery scale-revised: Measurement characteristics and diagnostic utility," *Arch. Phys. Med. Rehabil.*, vol. 85, no. 12, pp. 2020–2029, Dec. 2004, doi: 10.1016/j.apmr.2004.02.033.

[9] D. Kondziella, C. K. Friberg, V. G. Frokjaer, M. Fabricius, and K. Møller, "Preserved consciousness in vegetative and minimal conscious states: Systematic review and meta-analysis," *J. Neurol. Neurosurg. Psychiatry*, vol. 87, no. 5, pp. 485–492, May 2016, doi: 10.1136/jnnp-2015-310958.

[10] B. Rohaut, frédéric faugeras, and L. Naccache, "Neurology of consciousness impairments," in *Brain Disorders in Critical Illness: Mechanisms, Diagnosis, and Treatment*. Cambridge, U.K.: Cambridge Univ. Press, 2013, pp. 59–67, doi: 10.13140/2.1.2726.8804.

[11] C. Schnakers et al., "Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment," *BMC Neurol*, vol. 9, Jul. 2009, Art. no. 35, doi: 10.1186/1471-2377-9-35.

[12] A. Estraneo et al., "Multicenter prospective study on predictors of short-term outcome in disorders of consciousness," *Neurology*, vol. 95, no. 11, pp. e1488–e1499, Sep. 2020, doi: 10.1212/WNL.0000000000010254.

[13] S. Ballanti et al., "EEG-based methods for recovery prognosis of patients with disorders of consciousness: A systematic review," *Clin. Neurophysiol.*, vol. 144, pp. 98–114, Dec. 2022, doi: 10.1016/j.clinph.2022.09.017.

[14] P. Liuzzi et al., "Merging clinical and EEG biomarkers in an elastic-net regression for disorder of consciousness prognosis prediction," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 30, pp. 1504–1513, 2022, doi: 10.1109/TNSRE.2022.3178801.

[15] A. M. Owen, "The Search for Consciousness," *Neuron*, vol. 102, no. 3, pp. 526–528, May 2019, doi: 10.1016/j.neuron.2019.03.024.

[16] D. Kondziella et al., "European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness," *Eur. J. Neurol.*, vol. 27, no. 5, pp. 741–756, 2020, doi: 10.1111/ene.14151.

[17] A. Comanducci 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.*, vol. 131, no. 11, pp. 2736–2765, Nov. 2020, doi: doi: 10.1016/j.clinph.2020.07.015.

[18] B. Wutzl et al., "Narrative review: Quantitative EEG in disorders of consciousness," *Brain Sci.*, vol. 11, no. 6, Jun. 2021, Art. no. 697, doi: 10.3390/brainsci11060697.

[19] A. Duszyk-Bogorodzka, M. Zieleniewska, and K. Jankowiak-Siuda, "Brain activity characteristics of patients with disorders of consciousness in the EEG resting State paradigm: A review," *Front. Syst. Neurosci.*, vol. 16, 2022, Art. no. 654541, Accessed: Feb. 3, 2023. [Online]. Available: https://www.frontiersin.org/articles/10.3389/fnsys.2022.654541

[20] J. Leon-Carrion, J. F. Martin-Rodriguez, J. Damas-Lopez, J. M. Barroso y Martin, and M. R. Dominguez-Morales, "Brain function in the minimally conscious state: A quantitative neurophysiological study," *Clin. Neurophysiol.*, vol. 119, no. 7, pp. 1506–1514, Jul. 2008, doi: 10.1016/j.clinph.2008.03.030.

[21] D. Marinazzo et al., "Directed information transfer in scalp electroencephalographic recordings: Insights on disorders of consciousness," *Clin. EEG Neurosci.*, vol. 45, no. 1, pp. 33–39, Jan. 2014, doi: 10.1177/1550059413510703.

[22] A. A. Fingelkurts, A. A. Fingelkurts, S. Bagnato, C. Boccagni, and G. Galardi, "EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states," *Consciousness Cogn.*, vol. 21, no. 1, pp. 149–169, Mar. 2012, doi: 10.1016/j.concog.2011.10.004.

[23] J. Lechinger et al., "CRS-R score in disorders of consciousness is strongly related to spectral EEG at rest," *J. Neurol.*, vol. 260, no. 9, pp. 2348–2356, Sep. 2013, doi: 10.1007/s00415-013-6982-3.

[24] "Functional isolation within the cerebral cortex in the vegetative state: A nonlinear method to predict clinical outcomes - Marco Sarà, Francesca Pistoia, Patrizio Pasqualetti, Fabio Sebastiano, Paolo Onorati, Paolo M. Rossini, 2011." Accessed: May 2, 2024. [Online]. Available: https://journals.sagepub.com/doi/full/10.1177/1545968310378508

[25] O. Gosseries et al., "Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state," *Funct. Neurol.*, vol. 26, no. 1, pp. 25–30, 2011.

[26] M. Sarà and F. Pistoia, "Complexity loss in physiological time series of patients in a vegetative state," *Nonlinear Dyn., Psychol., Life Sci.*, vol. 14, no. 1, p. 1, 2010.

[27] L. Pollonini et al., "Information communication networks in severe traumatic brain injury," *Brain Topogr.*, vol. 23, no. 2, pp. 221–226, Jun. 2010, doi: 10.1007/s10548-010-0139-9.

[28] J. Leon-Carrion et al., "Synchronization between the anterior and posterior cortex determines consciousness level in patients with traumatic brain injury (TBI)," *Brain Res.*, vol. 1476, pp. 22–30, Oct. 2012, doi: 10.1016/j.brainres.2012.03.055.

[29] J.-R. King et al., "Information sharing in the brain indexes consciousness in noncommunicative patients," *Curr. Biol.*, vol. 23, no. 19, pp. 1914–1919, 2013.

[30] J. D. Sitt et al., "Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state," *Brain*, vol. 137, no. Pt 8, pp. 2258–2270, Aug. 2014, doi: 10.1093/brain/awu141.

[31] J. Toppi, D. Mattia, M. Risetti, R. Formisano, F. Babiloni, and L. Astolfi, "Testing the significance of connectivity networks: Comparison of different assessing procedures," *IEEE Trans. Biomed. Eng.*, vol. 63, no. 12, pp. 2461–2473, Dec. 2016, doi: 10.1109/TBME.2016.2621668.

[32] D. Wu, G. Cai, R. D. Zorowitz, Y. Yuan, J. Wang, and W. Song, "Measuring interconnection of the residual cortical functional islands in persistent vegetative state and minimal conscious state with EEG nonlinear analysis," *Clin. Neurophysiol.*, vol. 122, no. 10, pp. 1956–1966, Oct. 2011, doi: 10.1016/j.clinph.2011.03.018.

[33] S. Stefan et al., "Consciousness indexing and outcome prediction with resting-State EEG in severe disorders of Consciousness," *Brain Topogr.*, vol. 31, no. 5, pp. 848–862, Sep. 2018, doi: 10.1007/s10548-018-0643-x.

[34] S. Chennu et al., "Spectral signatures of reorganised brain networks in disorders of consciousness," *PLOS Comput. Biol.*, vol. 10, no. 10, Oct. 2014, Art. no. e1003887, doi: 10.1371/journal.pcbi.1003887.

[35] W. H. Curley, A. Comanducci, and M. Fecchio, "Conventional and investigational approaches leveraging clinical EEG for prognosis in acute disorders of consciousness," *Seminar Neurol.*, vol. 42, no. 3, pp. 309–324, Jun. 2022, doi: 10.1055/s-0042-1755220.

[36] R. Pauli, A. O'Donnell, and D. Cruse, "Resting-State electroencephalography for prognosis in disorders of consciousness following traumatic brain injury," *Front. Neurol.*, vol. 11, 2020, Art. no. 586945, doi: 10.3389/fneur.2020.586945.

[37] M. Song et al., "Prognostic models for prolonged disorders of consciousness: An integrative review," *Cellular Mol. Life Sci.*, vol. 77, no. 20, pp. 3945–3961, Oct. 2020, doi: 10.1007/s00018-020-03512-z.

[38] G. Teasdale and B. Jennett, "Assessment of coma and impaired consciousness. A practical scale," *Lancet*, vol. 304, no. 7872, pp. 81–84, Jul. 1974, doi: 10.1016/S0140-6736(74)91639-0.

[39] F. Lombardi, G. Gatta, S. Sacco, A. Muratori, and A. Carolei, "The Italian version of the coma recovery scale-revised (CRS-R)," *Funct. Neurol.*, vol. 22, no. 1, pp. 47–61, 2007.

[40] O. Mecarelli, *Clinical Electroencephalography*, 1st ed. Cham, Switzerland: Springer, 2019.

[41] L. A. Baccalá and K. Sameshima, "Partial directed coherence: A new concept in neural structure determination," *Biol. Cybern.*, vol. 84, no. 6, pp. 463–474, May 2001, doi: 10.1007/PL00007990.

[42] D. Yasumasa Takahashi, L. Antonio Baccal, and K. Sameshima, "Connectivity inference between neural structures via partial directed coherence," *J. Appl. Statist.*, vol. 34, no. 10, pp. 1259–1273, Dec. 2007, doi: 10.1080/02664760701593065.

[43] J. Toppi et al., "How the statistical validation of functional connectivity patterns can prevent erroneous definition of small-world properties of a brain connectivity network," *Comput. Math. Methods Med.*, vol. 2012, Aug. 2012, Art. no. e130985, doi: 10.1155/2012/130985.

[44] M. Rubinov and O. Sporns, "Complex network measures of brain connectivity: Uses and interpretations," *NeuroImage*, vol. 52, no. 3, pp. 1059–1069, Sep. 2010, doi: 10.1016/j.neuroimage.2009.10.003.

[45] D. J. Watts and S. H. Strogatz, "Collective dynamics of 'small-world' networks," *Nature*, vol. 393, no. 6684, pp. 440–442, Jun. 1998, doi: 10.1038/30918.

[46] V. Latora and M. Marchiori, "Efficient behavior of small-world networks," *Phys. Rev. Lett.*, vol. 87, no. 19, Nov. 2001, Art. no. 198701.

[47] S. Chennu et al., "Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness," *Brain*, vol. 140, no. 8, pp. 2120–2132, Aug. 2017, doi: 10.1093/brain/awx163.

[48] B. Schorr, W. Schlee, M. Arndt, and A. Bender, "Coherence in resting-state EEG as a predictor for the recovery from unresponsive wakefulness syndrome," *J. Neurol.*, vol. 263, no. 5, pp. 937–953, May 2016, doi: 10.1007/s00415-016-8084-5.

[49] K. Smitha et al., "Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks," *Neuroradiology J.*, vol. 30, no. 4, pp. 305–317, Aug. 2017, doi: 10.1177/1971400917697342.

[50] A. Soddu et al., "Resting state activity in patients with disorders of consciousness," *Funct. Neurol.*, vol. 26, no. 1, pp. 37–43, 2011.

[51] S. Ovadia-Caro et al., "Reduction in inter-hemispheric connectivity in disorders of consciousness," *PLoS ONE*, vol. 7, no. 5, 2012, Art. no. e37238, doi: 10.1371/journal.pone.0037238.

[52] V. Mäki-Marttunen, I. Diez, J. M. Cortes, D. R. Chialvo, and M. Villarreal, "Disruption of transfer entropy and inter-hemispheric brain functional connectivity in patients with disorder of consciousness," *Front. Neuroinform.*, vol. 7, 2013, Art. no. 24, doi: 10.3389/fninf.2013.00024.

[53] A. A. Fingelkurts, A. A. Fingelkurts, S. Bagnato, C. Boccagni, and G. Galardi, "Prognostic value of resting-state electroencephalography structure in disentangling vegetative and minimally conscious states: A preliminary study," *Neurorehabil. Neural Repair*, vol. 27, no. 4, pp. 345–354, May 2013, doi: 10.1177/1545968312469836.

[54] A. Piarulli, M. Bergamasco, A. Thibaut, V. Cologan, O. Gosseries, and S. Laureys, "EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness," *J Neurol*, vol. 263, no. 9, pp. 1746–1760, Sep. 2016, doi: 10.1007/s00415-016-8196-y.

[55] D. Rossi Sebastiano et al., "Significance of multiple neurophysiological measures in patients with chronic disorders of consciousness," *Clin. Neurophysiol*, vol. 126, no. 3, pp. 558–564, Mar. 2015, doi: 10.1016/j.clinph.2014.07.004.

[56] A. Thibaut et al., "Preservation of brain activity in unresponsive patients identifies MCS star," *Ann. Neurol.*, vol. 90, no. 1, pp. 89–100, Jul. 2021, doi: 10.1002/ana.26095.

[57] S. Haufe, S. Dähne, and V. V. Nikulin, "Dimensionality reduction for the analysis of brain oscillations," *NeuroImage*, vol. 101, pp. 583–597, Nov. 2014, doi: 10.1016/j.neuroimage.2014.06.073.

[58] G. Nolte, O. Bai, L. Wheaton, Z. Mari, S. Vorbach, and M. Hallett, "Identifying true brain interaction from EEG data using the imaginary part of coherency," *Clin. Neurophysiol.*, vol. 115, no. 10, pp. 2292–2307, Oct. 2004, doi: 10.1016/j.clinph.2004.04.029.

[59] J. Toppi et al., "Different topological properties of EEG-derived networks describe working memory phases as revealed by graph theoretical analysis," *Front. Hum. Neurosci.*, vol. 11, Jan. 2018, Art. no. 637, doi: 10.3389/fnhum.2017.00637.

Open Access provided by 'Università degli Studi di Roma "La Sapienza" 2' within the CRUI CARE Agreement