EEG-based quantitative measures to support the clinical diagnosis of disorders of consciousness

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***Abstract*—Severe acquired brain injury often leads to a disorder of consciousness (DoC) which can be classified as vegetative state (VS) or minimally consciousness state (MCS) according to its severity. The golden standard for DoC diagnosis is currently represented by the standardized Coma Recovery Scale Revised which, due to fluctuations in DoCs' vigilance, can lead up to 40% of misdiagnosis. EEG-based analyses have demonstrated promising results in DoC patients' assessment and quantitative EEG measures are candidates as a reliable instrument to support clinical diagnosis with high accuracy. Methodologies for spectral analysis and connectivity estimation were applied to EEG resting state data from 58 DoC patients clinically assessed as VS or MCS. Indices describing the global properties of the resting networks and the characteristics of power spectra resulted significantly different between the two groups of patients. The significant indices were used as features to train a classifier able to discriminate VS from MCS with performance metrics equal to 67% for accuracy and 85% for precision. These findings boost the promising role of EEG-based indices as valuable and reliable tool to support DoC clinical diagnosis.**

***Keywords*—Diagnosis, disorders of consciousness, connectivity analysis, spectral analysis.**

I. INTRODUCTION

PEOPLE who survive a severe brain injury, can suffer from disorders of consciousness (DoC), a clinical condition characterized by alteration in arousal (eye opening), and awareness (defined as the presence of nonreflexive behavior). Three main states can be included in DoC: coma, vegetative state (VS) and minimally conscious state (MCS). Coma is characterized by the total absence of both arousal and awareness, while VS patients show arousal, but they are unresponsive to external stimuli and only show reflexive behavior. MCS subjects, on the other side, demonstrate signs of awareness of themselves and the environment, but this condition is characterized by strong fluctuations [1]. The European Task Force has introduced the definition of "unresponsive wakefulness syndrome" (UWS) [2] to replace the term "vegetative state," although it has not been universally accepted [3]. For this reason, in this work we will use the double term VS/UWS for referring to that condition.

DoC classification is based on standardized neurobehavioral rating scales, among which Coma Recovery Scale Revised (CRS-R) is the most widely diffused and consists in 6 subscales evaluating auditory, visual, motor, oromotor, communication and arousal processes. Clinical scales represent the gold standard for DoC assessment. Although they represent a consistent and sensitive standard, clinical scales depend on behavioral responses, that can be affected by a multitude of factors, such as fluctuation of arousal, fatigue, pain, spasticity, to cite just few of them. Thus, the misdiagnosis rate is high and attested around 40% [4]. However, an accurate assessment is fundamental for DoC's diagnosis, prognosis and monitoring of treatment and rehabilitation effects [5].

The absence of quantitative measures for the diagnosis of DoC patients has motivated many researchers to find objective measures derived from brain signals as support for the clinical evaluation. Previous studies have performed EEG analyses of resting state acquisitions to investigate connectivity characteristics in DoC patients, but mainly using neuroimaging techniques (i.e., functional magnetic resonance imaging, fMRI). Results of this kind of studies demonstrated the correlation between the level of consciousness and the connections weight in the Default Mode Network (DMN), a circuit composed by specific brain areas active during rest condition and deactivated in attention-demanding tasks [6].

EEG shows invaluable advantages in comparison to other neuroimaging techniques, both at the theoretical and at the practical level: it allows to capture the dynamics of brain connectivity and its spectral distribution, by keeping it viable to handle severely disabled patients even with bedside testing, being therefore eligible for routine clinical application.

Previous studies have identified markers derived from a combination of connectivity estimators and graph theory able to classify MCS patients from VS/UWS and healthy subjects with an accuracy slightly above chance [7],[8].

Indeed, in this study a quantitative analysis of EEG recorded in resting condition was conducted to calculate spectral and connectivity indices that could be a reliable instrument to perform diagnosis in patients with disorders of consciousness.

II. MATERIALS AND METHODS

A. Participants

The study involved 58 patients admitted at the Post-Coma Unit of Fondazione Santa Lucia of Rome and diagnosed with DoC (29 males/29 females, mean age 45±16 yr, CRS-R score: 11±5, etiology: 22 TBI, 6 anoxic, 27 vascular, 3 other). According to their CRS-R scores, 40 out of 58 patients were assessed as MCS (19 males, 21 females, mean age: 46.85±16.03 yr, CRS-R score: 14±3), while the remaining 18 were diagnosed with VS/UWS (10 males and 8 females, mean age: 39.67±15.38 yr, CRS-R score: 5±2). 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). The present study protocol was approved by the local Ethics committee of Fondazione Santa Lucia (Prot. CE/PROG.603). Written informed consent was obtained by the patients' legal surrogates.

B. EEG recordings

EEG signals were acquired by means of 19 bridge electrodes (Micromed) positioned over patients' scalp according to 10-20 International System (reference on Fpz, ground on Oz). EEG was acquired in resting state condition for approximately 5 minutes with a sampling frequency equal to 250 Hz.

C. Pre-processing

Raw signals were band-pass filtered (1-20 Hz) to select the frequency band of interest and to remove the contribution of muscular artefacts. Independent Component Analysis (ICA) was used to remove ocular artefacts when eye-blinks were recognizable on the traces. Subsequently signals were segmented in epochs of 1 second duration. A threshold approach for artefacts removal was then applied to exclude trials exceeding in absolute value the amplitude of 100 μV. A random sample of 100 trials was extracted for each subject to provide an equal amount of data for each patient to perform further analyses.

D. Spectral Analysis

Spectral analysis was executed on pre-processed data of the midline electrodes (Fz, Cz, Pz) computing Power Spectral Density (PSD) by means of Welch periodogram (Hann windows of 1 second duration with no overlap). Five out of 58 patients were excluded from spectral analysis due to residual muscular component. Relative Power (RP) was calculated to evaluate the contribution of the single frequency bands (delta: 1-3 Hz, theta: 4-7 Hz, alpha: 8-13 Hz) to the global power.

E. Connectivity Analysis

Connectivity analysis was conducted estimating functional resting state network using Partial Directed Coherence (PDC) [9], a multivariate spectral estimator providing weight and direction about functional links connecting different time-series in specific scalp positions. PDC values were averaged in delta (1-3 Hz), theta (4-7 Hz) and alpha (8-13 Hz) bands and asymptotic statistics validation method was applied to assess the significance of each connection against chance level [10]. Four out of 58 patients were excluded from connectivity analysis since estimated networks showed density values inferior to 10%.

To evaluate global properties of the estimated networks, the following indices were calculated: clustering coefficient, path length and small-worldness. Clustering coefficient is a segregation index that quantifies the presence of functionally specialized clusters in the estimated network and investigates the prevalence of clustered connectivity around individual nodes. Path length is a measure of integration of the network and reflects the distance between nodes. Small-worldness describes how well the properties of segregation and integration are combined to create a network that presents both segregated modules and intermodular (integrating) links [11].

F. Statistical Analysis and Classification

Basing on the exclusion criteria applied to spectral and connectivity analyses that were mentioned before, spectral indices were evaluated for 14 out of 18 UWS patients and 39 out of 40 MCS, while connectivity indices were calculated for 18 UWS and 36 out of 40 MCS. Afterwards the spectral and connectivity indices evaluated for the two groups were statistically compared using an unpaired t-test (alpha equal to 0.05).

Measures that resulted statistically different between the two groups were deployed as features to train a Supported Vector Machines (SVM) classifier with linear kernel able to discriminate MCS and UWS classes. Data augmentation was applied to numerically inferior class to compensate for unbalanced dataset. Leave-one-subject-out was used as validation approach and for each subject classification performance indices were calculated (i.e., accuracy, precision, specificity, sensitivity, area under curve).

III. Results

A. Comparing spectral and connectivity indices between VS/UWS and MCS

Relative powers in all the three bands considered (delta, theta and alpha) resulted significantly different between the two groups of patients on Pz channel. Moreover, relative power evaluated in delta and theta bands obtained a significant p-value (<0.05) also on Fz channel. As shown in Fig. 1, relative power in delta band on Pz channel is significantly higher in VS than in MCS patients. Conversely, relative power in theta and alpha bands showed the opposite trend, being lower in VS/UWS patients than in MCS. No significant differences were found in relative powers evaluated on Cz channel for all the three bands.

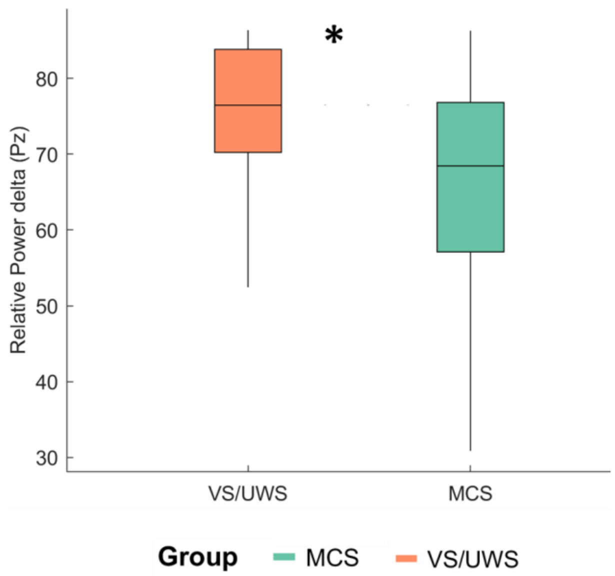

Fig. 1: Box plot representation of the statistical comparison of the relative power in delta band on Pz channel for VS/UWS group (in orange) and MCS group (in green). Statistically significant differences between the two groups are marked with the symbol *.

Statistical analysis applied to connectivity indices evidenced significant differences between the two groups for clustering coefficient and small-worldness, both in delta band.

As reported in Fig. 2, path length (Fig. 2, panel a) shows

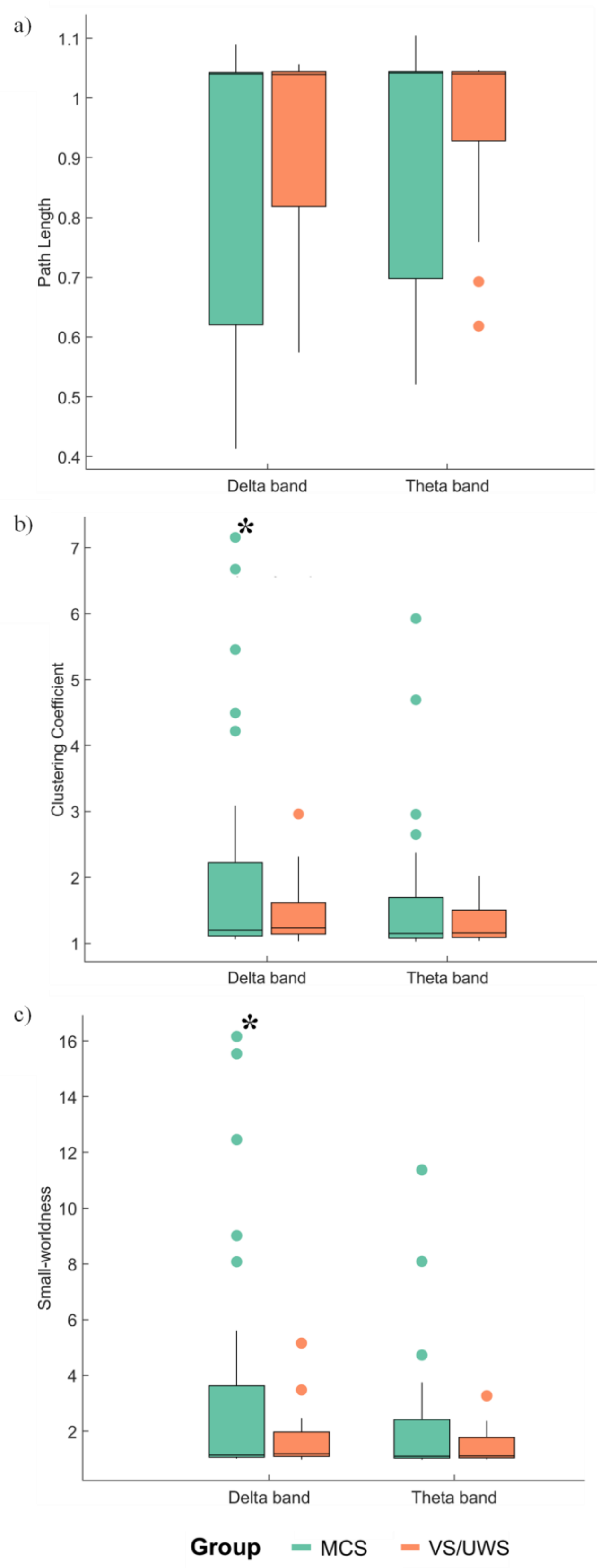

Fig. 2: Box plot representation of the statistical comparison of the connectivity indices distributions in delta and theta bands for VS/UWS group (in orange) and MCS group (in green): path length (panel a), clustering coefficient (panel b), small-worldness (panel c). Statistically significant differences between the two groups are marked with the symbol *.

significant differences between the two groups neither in delta nor in theta band, while both clustering coefficient (Fig. 2, panel b) and small-worldness (Fig. 2, panel c) evaluated in delta band are significantly lower in VS group. No significant p-values were obtained from statistical analysis of connectivity indices evaluated in theta and alpha bands.

B. EEG-based Classification of VS/UWS – MCS patients

Relative power on Pz channel, clustering coefficient and small-worldness, all evaluated in delta band and resulted as significant indices from statistical analysis, were used as features to train the SVM classifier. Figure 3 shows the values of the performance indices calculated for the classifier trained: the accuracy value obtained is equal to 67.35% with an AUC equal to 75%.

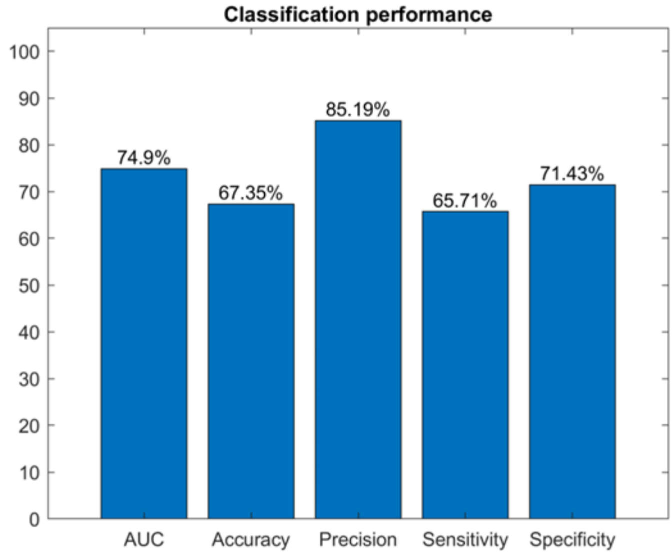

Fig. 3: Histogram reporting the performance of the SVM classifier with linear kernel trained using as features the following indices: relative power in delta band on Pz channel, clustering coefficient in delta band, small-worldness in delta band.

IV. Discussion

In this paper we aimed at providing quantitative and reliable indices, extracted from EEG resting state networks, to discriminate VS/UWS from MCS in order to corroborate the clinical/behavioral diagnosis of DoC patients.

Among the indices calculated small-worldness, clustering coefficient and relative spectral power on Pz channel, all evaluated in delta band, resulted as quantitative measures able to distinguish the two classes of patients. Indeed, these indices resulted significantly different between UWS/VS and MCS patients.

Previous EEG studies, based on graph theory indices extracted from connectivity networks at rest, have already pointed out the distinctive aspects of brain networks that characterize the DoC in comparison with healthy subjects and the correlations with their degree of behavioral responsiveness or hidden awareness [12].

According to the results obtained, clustering coefficient is significantly higher in MCS patients. This index quantifies the property of segregation of the estimated network. Segregation measures describe the presence in the network of densely interconnected groups of brain regions that are specialized in fulfilling common functions. Higher values of clustering coefficient witness the presence of clusters in functional networks [11]. Therefore, the results obtained evidence that resting state networks in MCS were characterized by higher communication efficiency and higher tendency to organize their structure in clusters in comparison with UWS/VS. Previous studies already evidenced the correlation between the re-emergence of strong connectivity hubs in brain network and increasing levels of consciousness [13].

Integration measures are the other important category of indices that describe the global properties of the estimated network and that represent the ability of the brain to integrate the information deriving from distributed regions. Lower values of path length represent a major functional integration among different brain regions and an efficient propagation of information in the network [11]. Although MCS patients showed lower values of path length, the difference between the distribution of values was not significant between the two groups, so this measure was not considerate crucial to discriminate the two classes.

An optimal network needs to balance functional integration and segregation and this capacity is described by small-worldness. Small-world networks can simultaneously support segregation (high clustering coefficient) and integration (low path length) and are characterized by small-worldness index values superior to 1 [11]. The analyses conducted evidenced higher values of small-worldness in MCS group. The presence of highly inter-connected hubs in patients with increasing level of consciousness are believed to contribute to create a small-world functional network in the brain [14].

Several prior studies already stated the ability of spectral indices to distinguish between UWS and MCS patients. UWS/VS patients have shown increased delta power but decreased alpha power, compared to the values calculated in MCS [15]. Theta power is not so well studied, but it was found to be higher in UWS patients compared to healthy controls [16], moreover a study reported that UWS patients had lower theta power when compared to MCS patients [17]. These results are all consonant to the ones obtained in the current study.

Since connectivity indices showed significant differences only in delta band, the significant spectral index chosen to train the classifier was relative power in delta band. Albeit the accuracy of the classifier implemented has margins of improvement, it nevertheless exceeded the accuracy of clinical assessment methods. This finding further strengthens the potential and the relevance that such surrogate measure of the consciousness disorders might have to improve clinical diagnosis of DoC patients.

V. Conclusion

This study suggests how quantitative EEG measures could be a valid instrument to support clinical diagnosis in patients suffering from disorders of consciousness. The analyses conducted indicate how surrogate measures of consciousness disorders based on EEG might allow to improve the accuracy of the gold-standard clinical instruments for diagnosis. This can be achieved with just few minutes of EEG signal recording without requiring any voluntary contribution by the patient.

In order to better the classification performance obtained, this study can be considered as a preliminary one, with the purpose of investigating more specific indices describing resting state networks and to test alternative classification approaches.

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