Proceedings of the
7th Graz Brain-Computer Interface Conference 2017 DOI: 10.3217/978-3-85125-533-1-89

EEG-BASED GRAPH THEORY INDICES 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 in vegetative state (VS) or minimally consciousness state (MCS) according to its severity. While the standardized Coma Recovery Scale Revised (CRS-R) is considered the gold-standard for the diagnosis of DOCs, fluctuations in the level of awareness and/or operator-dependence variation may hinder diagnostic accuracy (up to 40% of misdiagnosis for VS). Here we aimed at providing reliable EEG-based indices extracted from resting state networks that can corroborate clinical diagnosis with high level of accuracy, even in absence of behavioral signs of consciousness. Advanced methodologies for connectivity estimation and graph theory were applied to EEG resting state data from 15 DOC patients (2 groups: 6 VS and 9 MCS). Indices describing the global properties of the resting networks and the information flows between anterior and posterior brain regions resulted significantly different between the two groups. Moreover, they allowed the discrimination between VS from MCS with accuracy above 80%. These findings boost the role of EEG synthetic indices as valuable and reliable tool to support DOC clinical diagnosis.

INTRODUCTION

Disorders of Consciousness (DOCs) after severe acquired brain injury include, in the acute phase, coma and in the post-acute phase, vegetative state (VS) and minimally conscious state (MCS). The VS is a condition that follows coma, when the patient recovers vigilance (eyes opening), but not awareness, defined as the ability to interact with the surroundings, in spite of eyes opening and partial recovery of the sleep-wake circadian cycle [1]. More recently, 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]. Here, we will use the term VS/UWS. The MCS has been described as a condition in which the patient recovers eye tracking ability or fluctuating commands, while remaining unable to communicate [4].

The current gold-standard in diagnosis of DOC patients is the JFK Coma Recovery Scale Revised (CRS-R) which allows the clinical assessment of residual visual, auditory, motor, verbal functions, patients’ communication ability and awareness [5]. Reliance on behavioral assessment presents however, significant challenges and may lead to a misdiagnosis up to 40% (in VS) with evident impact on DOCs assistance and rehabilitation [6].

In light of this, several studies investigating neuroelectrical and hemodynamical brain signals at rest and during batteries of auditory, visual and tactile stimuli have been conducted in DOC patients in order to isolate quantitative markers of awareness independently of behavior [7]–[9]. The most promising studies appears to be those based on the analysis of alterations in DOC resting state networks, particularly in the so-called Default Mode Network, with respect to healthy subjects [10].

Hemodynamical and neuroelectrical measures have recently gained growing interest as a tool that may—in perspective—support the diagnosis of patients with different DOC by circumventing the need for behavioral responses. The networks defined by the statistical relationship between different signals (and their properties at different frequencies) can be seen as indirect correlates of the information processing by the patient’s brain.

EEG shows invaluable advantages with respect 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 [11], [12].

In this study, we employed Partial Directed Coherence, as spectral multivariate connectivity estimator [13] combined with asymptotic statistic method to assess patterns of connectivity [14] and graph theory to extract EEG indices describing the topology of

 DOI: 10.3217/978-3-85125-533-1-89

resting state networks in DOC [15]. As such, the combination of these computational methods was demonstrated to provide accurate, reliable and repeatable patterns in different experimental conditions and under different levels of signals quality [16]. The aim was to provide EEG-based indices to accurately discriminate/classify between different DOCs.

MATERALS AND METHODS

Participants: Fifteen patients were included in the study (age: 50±16 years, 8 males; lesions: 5 left, 5 right, 5 bilateral; etiology: 7 stroke and 8 traumatic brain injury). All the patients were recruited at the post coma unit of the Neurorehabilitation Hospital "Fondazione Santa Lucia," Rome, Italy. According to their CRS-R scores, patients were divided in two groups: 6 VS/UWS and 9 MCS. No significant differences between the two groups were found in terms of age, gender, and lesion site. One MCS subject was excluded from the analysis because of the presence of artifacts in EEG traces.

Scalp EEG recordings: All patients were subjected to an experimental session including EEG recordings during 2 minutes of eyes-closed resting condition (19 electrode cap, positioned according to 10-20 International System as used in clinical routine, reference on both earlobes and ground at left mastoid, sampling frequency of 250 Hz, g.USBamp amplifier, Guger Technologies, Austria).

Connectivity Analysis and graph theory: EEG signals were downsampled to 100 Hz and band pass filtered at 1–45 Hz. EEG traces were segmented in epochs of 1s length and then subjected to PDC estimation.

PDC is a is a full multivariate spectral measure used to determine the directed influences between pairs of signals in a multivariate dataset. Let us suppose that the following multivariate autoregressive (MVAR) process is an adequate description of the dataset Y:

$$\sum_{k=0}^{p} A(k)Y(t-k) = E(t) \quad (1)$$

Where Y(t) is the data vector in time, E(t) = [e1(t),…,eN(t)]T is a vector of multivariate zero-mean uncorrelated white noise processes, A(1),A(2),…,A(p) are the NxN matrices of model coefficients, and p is the model order. PDC can be computed as follows [13]:

$$\pi_{ij}(f) = \frac{\left|A_{ij}(f)\right|^2}{\sum_{m=1}^{N}\left|A_{mj}(f)\right|^2} \quad (2)$$

where $A_{ij}(f)$ represents the frequency version of the ij entry of matrix A.

The estimated PDC values were averaged in five frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–25 Hz), and gamma (26–40 Hz).

PDC significance was assessed against null-case by means of asymptotic statistics approach with a significance level of 5%. Such approach allows to derive the probability distribution of the null-case squared PDC estimator (the χ^2 distribution), by knowing its asymptotic variance [14], [16].

To compute indices describing the main local and global properties of the investigated patterns, we adopted measures derived from a graph theoretical approach [17], computed on the adjacency matrix *G* resulting from the assessment procedures [15]. In particular, we considered the following indices: i) ant/post asymmetry, anterior density, ant/post influence for describing the involvement of anterior areas with respect to the posterior ones, ii) inter-hemispheric connections, left/right divisibility, left/right modularity for describing the information exchange between left and right hemispheres [16] iii) clustering, global efficiency, local efficiency, path length for characterizing the global properties of the network such as the efficiency in communication or the tendency to create clusters [17].

Statistical analysis and classification: An independent samples t-test was performed (significance level 0.05, corrected by means of False Discovery Rate) between the indices extracted from VS/UWS and MCS networks. To check whether such indices were able to characterize each individual patient, we built a support vector machine (SVM) classifier with linear kernel, using as features the indices resulted as statistically different between VS/UWS and MCS. The classifier was built for each couple of indices and each frequency band. We employed a leave-one-out cross-validation approach, testing one subject each time. The corresponding classifier training was performed on two groups of patients of the same size. As a performance parameter, we computed the percentage of subjects whose state has been correctly classified.

Finally, the brain connectivity indices were correlated (Spearman correlation, $p<0.05$) with the clinical (CRS-R) scores. False discovery rate correction was used to correct for multiple correlations.

RESULTS

As reported in Fig. 1, (panel a), we found significantly higher values of ant/post asymmetry, ant/post influence, and anterior density in MCS patients with respect to VS/UWS as estimated in delta band of frequency. The ant/post asymmetry and ant/post influence indices were also significantly different between VS/UWS and MCS, in favor of MCS, in the theta band of frequency (Fig.1, panel a). Altogether, these results indicated a *lower* functional involvement of the frontal regions in VS/UWS patients as indicated by negative values of these indices in that experimental group. No significant differences were found between the two groups as for the indices of functional interhemispheric communication, namely the inter-hemispheric connections, left/right divisibility, left/right modularity (Fig.1, panel b) in both delta and theta bands. Regarding global properties of the resting state networks (Fig.1, panel c), we found significantly higher values of clustering coefficient and local efficiency and lower values of path length in MCS with respect to VS/UWS only in delta band.

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Table1 - Classification accuracy obtained using as features graph indices derived from DOC's resting state connectivity networks in delta band. A SVM classifier with linear kernel and three support vectors was built for comparing VS/UWS and MCS for each combination of graph indexes (reported on x- and y-axis). Classification accuracies above 70% were highlighted in bold.

	Ant/Post Asym	Ant Density	Ant/Post Infl	IHC	L/R div	L/R mod	Clust	Glob Eff	Loc Eff	Path Length
Ant/Post Asym	---	68,9	**78,5**	**73,7**	**78,8**	**73,4**	**81**	68,4	**82**	**82,8**
Ant Density	---	---	58,8	**76,4**	68,6	66,7	**70,7**	**79,3**	59,1	69,6
Ant/Post Infl	---	---	---	**78,5**	**75,5**	**75,3**	**72,7**	**73,5**	**74,7**	**73,3**
IHC	---	---	---	---	61,9	49	69	**70**	58,2	50,6
L/R_div	---	---	---	---	---	26	50,1	48,9	69,3	69,8
L/R_mod	---	---	---	---	---	---	43,2	42,4	56,5	39,4
Clust	---	---	---	---	---	---	---	63,4	51,5	64,5
Glob Eff	---	---	---	---	---	---	---	---	41,9	46,1
Loc Eff	---	---	---	---	---	---	---	---	---	54,8
Path Length	---	---	---	---	---	---	---	---	---	---

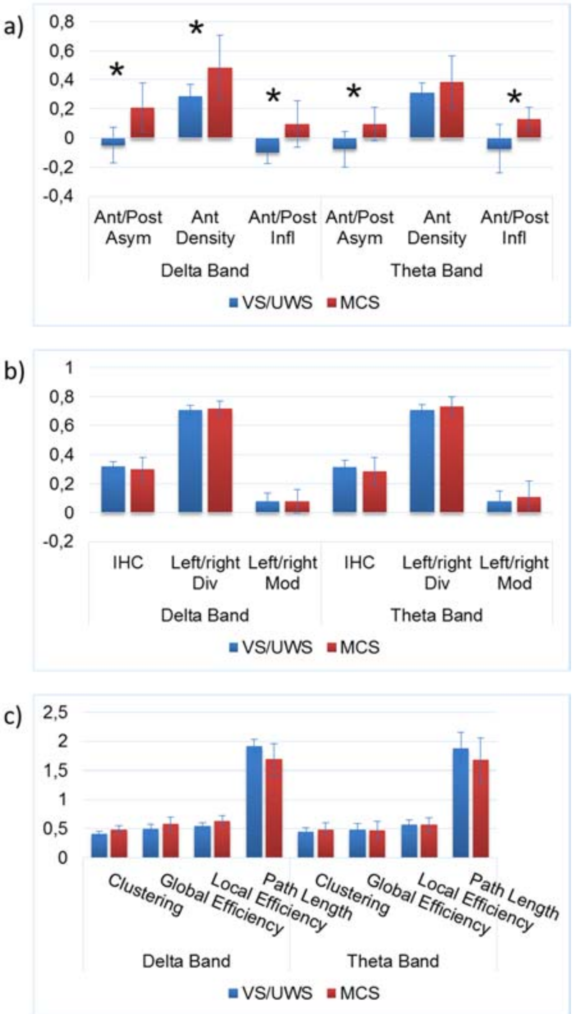

Figure 1: Bar diagrams reporting results related to the graph indices extracted separately for VS/UWS and MCS in delta and theta bands. Indices are grouped as follows: anterior/posterior (panel a), left/right (panel b), global indices (panel d). P-values associated to the statistical comparison between VS and MCS are reported for each index (independent samples t-test). In bold, values related to an alpha = 5% ($P < 0.05$).

No significant differences were found in the other bands for all the three groups of indices.

All the graph indices were used, in couples, as features to feed the SVM classifier. We built a classifier for each pair of indices (45 pairs in total) and two frequency bands (delta and theta). Results are reported in Table1. In particular, we found that accuracy above 70% was obtained only when the couple included indices such as those relative to functional communication between anterior and posterior areas and to the global properties of the networks. Worth of note are the accuracies above 80% obtained considering as features the ant/post asymmetry and tree global indices (clustering, local efficiency and path length). The accuracy obtained in theta band resulted lower than that in delta band.

Regarding the results of the Spearman correlation between the CRS-R scores and the ant/post asymmetry in the delta band. A significant positive correlation (R=0.6, p=0.024) between the ant/post asymmetry index and the CRS-r scores was observed only in the delta band.

No statistical correlations were found for the other indices in all frequency bands.

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.

According to our findings, the main differences found between VS/UWS and MCS can be quantified by 2 classes of indices: i) those describing the relationship between anterior and posterior areas of the brain and ii) those describing global properties of resting state networks such as efficiency and tendency to create clusters. In particular, VS/UWS's resting state networks present a reduced connectivity in frontal regions of the brain and a decrease in the communication flows going from the anterior to the posterior regions with respect to MCS. This is in line with previous studies pointing out in VS/UWS patients a deactivation of areas related to Default Mode Networks (including anterior cingulate cortex and medial pre-frontal cortex) and a reduction of the fronto-parietal connections [18], [19]. Furthermore, resting state networks in MCS were characterized by higher communication efficiency and higher tendency to

 DOI: 10.3217/978-3-85125-533-1-89

organize their structure in clusters with respect to VS/UWS as underlined by the significant differences in clustering, local efficiency and path length indices. Finally, most of the significant results were found in slow frequency bands (delta and theta), which have been related to cognitive tasks [20] and to different unconsciousness levels [21]. Overall, we speculate that this could reflect a global *deterioration* of the resting state networks in VS/UWS patients.

Previous EEG studies based on graph theory indices extracted from connectivity networks at rest, have already pointed out the distinctive aspects of DOCs' brain networks with respect to healthy subjects also providing correlations of resting state networks with the degree of behavioral responsiveness or hidden awareness in DOCs [22]. However, the characterization of DOC's resting state networks has been made only on the basis of global indices, such as clustering and path length, which give information about general properties of the networks. In this paper, we firstly confirmed what already found in terms of global properties of DOCs' networks. Then, we provided information about the spatial reorganization of DOCs' resting state netwroks induced by the brain injury. In particular, we employed indices describing the level and direction of information flow between anterior and posterior areas and between the two hemispheres. Regarding the global indices, we found results similar to those in [22] even considering a reduced number of electrodes (19 instead of 32). The simplification of the experimental setup without any loss of accuracy in the DOCs characterization is an important issue which has to be addressed if we are interested in employing such indices in the clinical diagnosis of DOCs.

Notably, the ant/post asymmetry index values appear to vary as function of the CRS-R scores. As yet, the same set of indices (in couple) was also reliable in 2-class discrimination analysis, that is VS/UWS and MCS were classified with up to 80% of accuracy. This finding further strengthens the relevance that such surrogate measure of the consciousness disorders might have to improve clinical diagnosis of DOC patients.

Once our findings would be confirmed in a larger group of patients we will move from a supervised approach where the classifier is trained on the basis of the results of CRS-R scale to an unsupervised approach entirely data driven in order to remove the dependence of the results on the diagnosis provided by CRS-R scale.

CONCLUSION

Our findings, if confirmed in a larger group of DOC patients, 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, provide that these findings are confirmed in a larger cohort of DOCs.

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