DIRECTED INFORMATION TRANSFER IN SCALP ELECTROENCEPHALOGRAPHIC RECORDINGS: INSIGHTS ON DISORDERS OF CONSCIOUSNESS

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Abstract

Introduction: The neural mechanisms underlying electrophysiological changes observed in patients with disorders of consciousness following a coma remain poorly understood. The aim of this article is to investigate the mechanisms underlying the differences in spontaneous electroencephalography between patients in vegetative/unresponsive wakefulness syndrome, minimally conscious state, emergence of the minimally conscious state and age-matched healthy control subjects.

Methods: Forty recording of spontaneous scalp electroencephalography were performed in 27 patients who were comatose on admission, and on healthy controls. Multivariate Granger Causality and Transfer Entropy were applied on the data.

Results: Distinctive patterns of putative bottlenecks of information were associated to each conscious state. Healthy controls are characterized by a greater amount of synergetic contributions from duplets of variables.

Conclusion: A novel set of measures was tested to get a novel insight on the pattern of information transfer in a network of scalp electrodes in patients with disorders of consciousness.

Keywords: electroencephalography, vegetative state, unresponsive wakefulness syndrome, minimally conscious state, transfer entropy, Granger causality.

1. **INTRODUCTION**

The neural mechanisms underlying electrophysiological changes observed in patients with disorders of consciousness (DOC) following a coma remain poorly understood. The vegetative state, recently renamed the unresponsive wakefulness syndrome (VS/UWS), is a state of preserved arousal without awareness of self and surrounding [1,2]. The minimally conscious state (MCS) is a state characterized by inconsistent but clearly discernible behavioral evidence of consciousness, and emergence from MCS occurs when patients regain functional communication or functional use of objects (EMCS)[3]. In this article, the mechanisms underlying the differences in spontaneous electroencephalography (EEG) will be investigated with the aim to objectively measure difference in cerebral activity related to the state of consciousness. With the advent of EEG technology, the computation of complex parameters has been made possible and measuring directed interactions in neuroimaging data in terms of information transfer is one of the promising approach, which is mathematically treatable and amenable to encompass several analytical methods.

Determining how the brain is connected is crucial in order to understand how it works. Each time we record brain activity we can monitor the activity at the nodes of a network. To gain a better understanding of which neurophysiological processes are linked to which brain mechanisms, structural connectivity in the brain can be complemented by the investigation of statistical dependencies between distant brain regions (functional connectivity), or by the development of models aiming at elucidating drive-response relationships (effective connectivity)[3]. Advances in imaging techniques guarantee an immediate improvement in our knowledge of structural connectivity. A constant computational and modeling effort has to be done in order to optimize and adapt functional and effective connectivity to the qualitative and quantitative changes in data and physiological applications. The paths of information flow throughout the brain can shed light on its functionality in healthy and pathological conditions.

Concerning effective connectivity, two main families of methods exist: those purely data-driven, identified as Granger Causality[4], and the biologically inspired ones, named Dynamical Causal Models[5]. In addition to these model-based approaches, Transfer Entropy[6] has emerged in the last years as a powerful alternative. This approach is rooted in information theory, and measures the rate of information flow between two variables, as a violation of the Markov property. An important characteristic of this measure is that it does not rely on any model.

It is worth to note that Granger causality is a measure of dynamical connectivity, and is not meant toevaluate actual causality, which requires an intervention on the system, such as Transcranial Magnetic Stimulation (TMS)[7].

Recently, it has been proven that Granger Causality and Transfer Entropy are equivalent for Gaussian variables[7], and for other quasi-Gaussian distributions[8]. Under this approximation, Transfer Entropy can be evaluated from the covariance matrix, and a numerically and analytically convenient framework can be established.

In this study, we propose to use this framework to look at the patterns of information transfer between electroencephalographic (EEG) signals recorded on the scalp of patients with DOC as well as in age-matched healthy control subjects. In particular, we will investigate two quantities derived in the framework described above. The first one relies on the fact that each node of a complex network can handle a limited amount of information. In information transfer networks, this results in a peculiar pattern describing the overall balance of information through a node, in which the distribution of ongoing information is wider than the distribution of incoming information. This indicates the likelihood of a node to become a possible “bottleneck” of information flow[9]. The second quantities regard the joint role of groups of variables in the prediction of a future state of the system. The standard formulations of Granger Causality and Transfer Entropy evaluate how much each individual source variable influences the future of a target one. But what happens if the putative source of information is constituted by a group of variables? Is their contribution as a whole greater than the sum of the individual contributions, i.e. are the variables synergetic? Or conversely are they redundant, i.e. the joint contribution is smaller than the sum of the individual contributions? The aim of the study is to use a recently developed methodology to group the EEG channels according to their informational content and their joint role in predicting the future of other channels in patients with DOC as compared to healthy subjects.

2. METHODS

2.1 Clinical assessment

The study was prospectively performed in 21 patients who were comatose on admission (aged 46±25 years; 13 males). Repeated behavioral measurements of consciousness were obtained by trained, experienced neuropsychologists using the Coma Recovery Scale-Revised (CRS-R)[10]. This scale has been specifically developed to differentiate between patients in UWS from MCS, and consists of six subscales: auditory, visual, motor and oromotor/verbal functions as well as communication and level of arousal. Repeated evaluations were carried out in order to obtain a stable clinical diagnosis and to avoid misdiagnosis due to fluctuations in responsiveness.

A total of 26 recordings for which several good quality segments were available for all the 19 10-20 channels were retained for the present study, and 3 patients were assessed more than one time. As assessed by the CRS-R, one patient was recorded while recovering consciousness and evolving from VS/UWS, through MCS to EMCS. Two patients were assessed during MCS and EMCS and the last patient was assessed in VS/UWS and in EMCS. The total sample consisted of 11 recordings in VS/UWS, 10 in MCS and 5 in EMCS. Etiology was traumatic in 12 patients; the non-traumatic cases (n=9) comprised patients with post-ischemic or hemorrhagic stroke (n=6), anoxic-ischemic encephalopathy (n=1) and subarachnoid hemorrhage (n=2). Patients were assessed free of centrally-acting drugs or neuromuscular function.

Scalp EEG at rest was also recorded from a matched group of 10 healthy controls (45±22 years old; 4 males).

The study was approved by the Ethics Committee of the Medicine Faculty of the University of Liege. Informed consents were obtained by the patients’ legal surrogates and by the patients when they were able to communicate.

N	Clinical diagnosis	Gender	Age	Etiology	Time since onset (days)
1	VS/UWS 1	M	19	trauma	172
2	VS/UWS 2	M	81	stroke	19
3	VS/UWS 3	M	67	stroke	247
4	VS/UWS 4	F	15	anoxia	23
5	VS/UWS 5	M	68	trauma	21
6	VS/UWS 6	F	43	stroke	20
7	VS/UWS 7	M	13	trauma	259
8	VS/UWS 8	F	26	trauma	808
9	VS/UWS 9	F	77	stroke	25
10	MCS 1	F	54	trauma	3220
11	MCS 2	M	72	stroke	38
12	MCS 3	M	29	trauma	2545
13	MCS 4	F	62	stroke	20
14	MCS 5	M	20	trauma	1334
15	MCS 6	M	19	trauma	191
16	MCS 7	M	46	trauma	9598
17	EMCS 1	M	23	trauma	422
18 (a)	VS/UWS 10	F	60	subar hem	31
	MCS 8				46
	EMCS 2				74
19 (b)	VS/UWS 11	M	16	trauma	12
	EMCS 3				41
20 (c)	MCS 9	M	77	trauma	16
	EMCS 4				59
21 (d)	MCS 10	F	76	subar hem	28
	EMCS 5				70

Table 1: the patients used in this study

2.2 EEG acquisition

Spontaneous EEG recordings of 5-minute epochs were obtained during a resting state condition. Patients were awake and were seated on their beds. The arousal facilitation protocol[11] was performed before the recording to ensure a high level of arousal. EEG was recorded with a 60-channel transcranial magnetic stimulation (TMS) -compatible amplifier (Nexstim; Helsinki, Finland). Electrode impedance was kept below 5kΩ. EEG signals were referenced to an additional electrode on the forehead, filtered (0.1–500Hz) and sampled at 1450Hz. Eye movements were also recorded with two additional electrodes placed near the eyes. EEG and TMS-EEG data of 17 of the patients reported in this study have been previously published elsewhere[12].

2.3 EEG analyses

For the current study, 19 scalp channels selected according to the 10-20 scheme were used; the data were resampled at 145 Hz, and the recordings from each subject were divided in several artifact-free segments of 5 seconds each.

A) MULTIVARIATE GRANGER CAUSALITY AND INFORMATION BOTTLENECKS

Multivariate Granger causality is a well-established approach to recover directed interactions from the dynamics of a group of simultaneously recorded variables.

Let's consider $n+1$ time series $\{x_\alpha(t)\}_{\alpha=0,\ldots,n}$. The lagged state vectors are denoted

$$Y_\alpha(t) = (x_\alpha(t-m), \ldots, x_\alpha(t-1)), \tag{1}$$

m being the order of the model, which can be determined using a standard cross-validation scheme. Let $\varepsilon(x_\alpha|Y)$ be the mean squared error prediction of x_α on the basis of all the vectors Y, corresponding to linear regression. The multivariate Granger Causality index $c(\beta \to \alpha)$ is defined as follows: consider the prediction of x_α on the basis of all the variables but Y_β and the prediction of x_α using all the variables, then the Granger causality is given by the variation of the error in the two conditions, i.e.

$$c(\beta \to \alpha) = \ln \frac{\varepsilon(x_\alpha|Y\backslash Y_\beta)}{\varepsilon(x_\alpha|Y)}. \tag{2}$$

The Granger Causality was first evaluated using the selection of significant eigenvalues, as described in Marinazzo et al.[13] to address the problem of overfitting. In the Gaussian approximation, this quantity is twice the transfer entropy, equal to $I\{x_\alpha; Y_\beta|Y\backslash Y_\beta\}$, and Granger causality can be interpreted in terms of information transfer.

The way in which information flows through a complex network is related to both the capacity of the nodes and to the structure of the network itself. This constraint suggests that information transfer networks should exhibit some topological evidences of the law of diminishing marginal returns[14], a fundamental principle of economics which states that when the amount of a variable resource is increased, while other resources are kept fixed, the resulting change in the output will eventually diminish[15]. This results in a peculiar pattern of the information flow between nodes: the distribution of the outgoing information is characterized by a fat tail, while the average incoming information transfer does not depend on the connectivity of the node. In the proposed model, the units at the nodes of the network are characterized by a transfer function that allows them to process just a limited amount of the incoming information. In this case, a possible way to quantify the law of the diminishing marginal returns can be the discrepancy of the distributions, expressed as the ratio of their standard deviations, that here indicated as R.

B) IDENTIFICATION OF IRREDUCIBLE SUBGRAPHS

Information theoretic treatment of groups of correlated degrees of freedom can reveal their functional roles as memory structures or those capable of processing information[16]. Information quantities reveal if a group of variables may be mutually redundant or synergetic[17,18]. Most approaches for the identification of functional relations among nodes of a complex networks rely on the statistics of motifs, subgraphs of *k* nodes that appear more abundantly than expected in randomized networks with the same number of nodes and degree of connectivity[19]. A formal expansion of the transfer entropy to put in evidence irreducible sets of variables which provide information for the future state of the target has been proposed by Marinazzo et al.[13]. Multiplets characterized by a high value, unjustifiable by chance, will be associated to informational circuits present in the system, with an informational character (synergetic or redundant) which can be associated to the sign of the contribution.

The fundamental ideas behind this approach are reported in the following lines. Given a stochastic variable X and a family of stochastic variables $\{Y_k\}_{k=1}^{n}$, we can define the mutual information I(X;{Y}) as the difference between S(X), the entropy of X, and S(X|{Y}), the same entropy conditioned to {Y}. The following expansion for the mutual information has been derived in Bettencourt et al.[20]:

$$S(X|\{Y\}) - S(X) = -I(X;\{Y\}) =$$
$$= \sum_i \frac{\Delta S(X)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(X)}{\Delta Y_i \Delta Y_j} + \cdots + \frac{\Delta^n S(X)}{\Delta Y_i \dots \Delta Y_n}, \tag{3}$$

where the variational operators are defined as

$$\frac{\Delta S(X)}{\Delta Y_i} = S(X|Y_i) - S(X) = -I(X;Y_i),$$
$$\frac{\Delta^2 S(X)}{\Delta Y_i \Delta Y_j} = -\frac{\Delta I(X;Y_i)}{\Delta Y_j} = I(X;Y_i) - I\left(X;Y_i \middle| Y_j\right), \tag{4}$$

and so on for the higher order terms.

Now, let us consider again the variables introduced in the previous paragraph and their state vectors. Firstly, expansion (4) can be used to model the statistical dependencies among the x variables at equal times. Considering x_0 as the target time series the first terms of the expansion are

$$W_i^0 = I(x_0;x_i) \tag{5}$$

for the first order,

$$Z_{ij}^0 = I(x_0;x_i) - I\left(x_0;x_i \middle| x_j\right) \tag{6}$$

for the second order, and so on for higher order terms.

In order to measure to what extent the remaining variables contribute to specify the future state of x_0, in Marinazzo et al.[13] it was proposed to consider:

$$S(x_0|\{Y_k\}_{k=1}^{n}) - S(x_0) =$$
$$\sum_i \frac{\Delta S(x_0)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(x_0)}{\Delta Y_i \Delta Y_j} + \cdots + \frac{\Delta^n S(x_0)}{\Delta Y_i \dots \Delta Y_n}. \tag{7}$$

Furthermore, in order to remove shared information due to common history and input signals, it is necessary to condition on the past of x_0, i.e. Y_0. This is achieved by introducing the conditioning operator $\mathcal{C}_{Y_0}$:

$$\mathcal{C}_{Y_0} S(X) = S(X|Y_0) \tag{8}$$

which allows to obtain an expansion of the transfer entropy as follows:

$$S(x_0|\{Y_k\}_{k=1}^{n}, Y_0) - S(x_0|Y_0) =$$

$$-I(x_0;\{Y_k\}_{k=1}^{n}|Y_0) = \sum_i \frac{\Delta S(x_0|Y_0)}{\Delta Y_i} + \sum_{i>j} \frac{\Delta^2 S(x_0|Y_0)}{\Delta Y_i \Delta Y_j} + \cdots + \frac{\Delta^n S(x_0|Y_0)}{\Delta Y_i \dots \Delta Y_n}. \tag{9}$$

The variations at every order in the above expansion are symmetrical under permutations of the Y_i. Moreover statistical independence among any of the Y_i results in vanishing contribution to that order: each nonvanishing term accounts for an irreducible set of variables providing information for the prediction of future values of the target.

An important property of the expansion is that the sign of nonvanishing terms reveals the informational character of the corresponding set of variables: a negative sign indicates that the group of variables contribute with more information, than the sum of its subgroups, to the state of the target (synergy), while positive contributions correspond to redundancy.

The first order terms in the expansion are given by:

$$A_i^0 = \frac{\Delta S(x_0|Y_0)}{\Delta Y_i} = -I(x_0;Y_i|Y_0), \tag{10}$$

and coincide (with opposite sign) with the bivariate transfer entropies $i \to 0$. The second order terms are

$$B_{ij}^0 = I(x_0;Y_i|Y_0) - I(x_0;Y_i|Y_j,Y_0) \tag{11}$$

and describe the duplets of variable that contribute jointly to the future of the target, in a redundant ($B_{ij}^0 > 0$) or synergetic ($B_{ij}^0 < 0$) way.

Another important point is how to get a reliable estimate of conditional mutual information from data. In this work, the assumption of Gaussianity is adopted and we use the exact expression that holds in this case[7] and reads as follows. Given multivariate Gaussian random variables *X*,*W* and *Z*, the conditioned mutual information is

$$I(X;W|Z) = \frac{1}{2}\ln\frac{|\Sigma(X|Z)|}{|\Sigma(X|W \oplus Z)|}, \tag{12}$$

where $|.|$ denotes the determinant, and the partial covariance matrix is defined

$$\Sigma(X|Z) = \Sigma(X) - \Sigma(X,Z)\Sigma(Z)^{-1}\Sigma(X,Z)^{\top} \tag{13}$$

in terms of the covariance matrix $\Sigma(X)$ and the cross covariance matrix $\Sigma(X,Z)$; the definition of $\Sigma(X|W \oplus Z)$ is analogous.

In the present study a model order $m = 5$ was selected according to leave-one-out crossvalidation[21].

3 RESULTS

3.1 Information bottlenecks

For all the groups of subjects, the distribution of the values of outgoing Granger Causality is wider than the distribution for incoming values (figure 1).

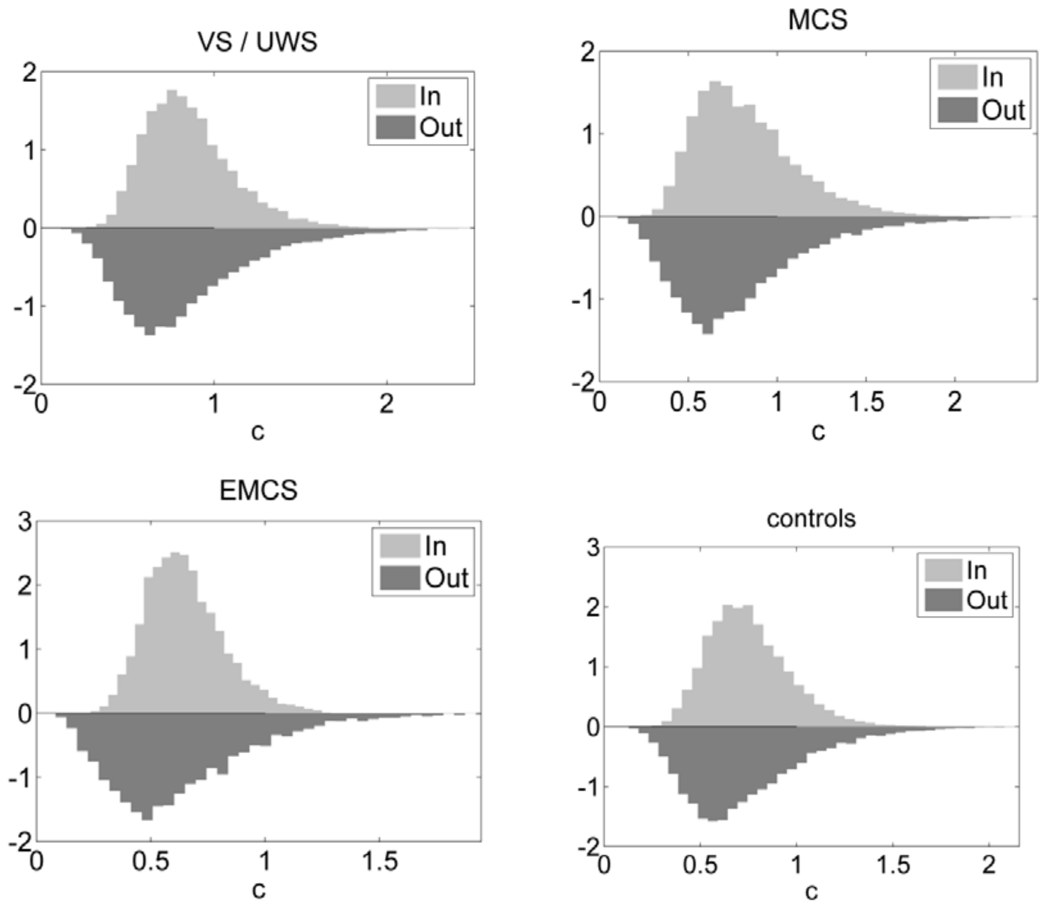
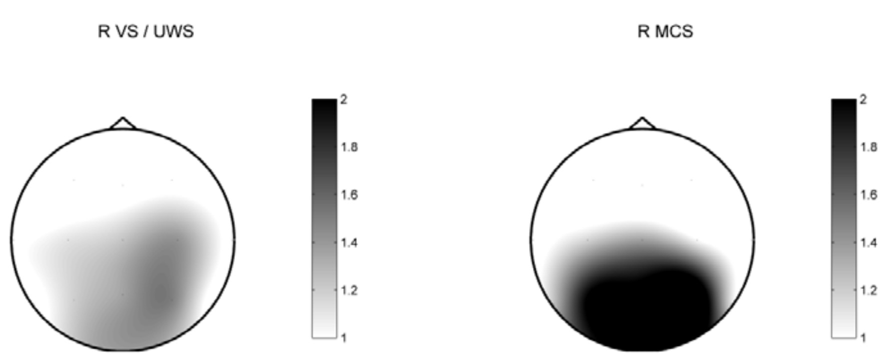


Figure 1: Distribution of outgoing and incoming values of multivariate Granger Causality (c).

The spatial modulation of this pattern shows substantial differences across the groups.

In the group of VS/UWS, the central, temporal and occipital electrodes display evidence of dissymmetry between incoming and outgoing information. Moving to MCS, and then to EMCS groups, the bottleneck regions get confined towards more occipital areas, while for healthy controls the areas with bigger disparity between outgoing and incoming information are in the lateral parietal electrodes (figure 2), as previously reported[9].



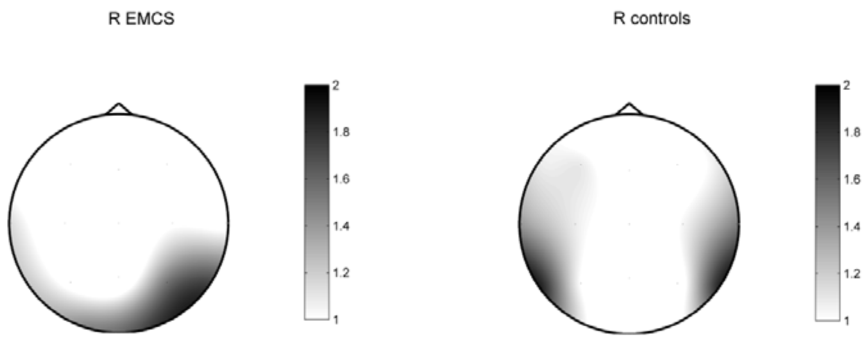


Figure 2: Topology of the values of R, the ratio between the width of the distribution of outgoing information and incoming information values.

3.2 Identification of informative multiplets

In this study, we evaluated exactly the first two terms of the expansion of the Transfer Entropy, that is the bivariate Transfer Entropies and the duplets of variables characterized by a significant contribution. For each dataset, we also generated a null distribution randomizing the order of the target time series.

The overall balance between synergy and redundancy was computed for each subject by summing all the contributions whose magnitude was greater than the 100th percentile of the null distribution.

The difference between groups was assessed by performing the Kruskal Wallis one-way ANOVA on the distributions of the values of net synergetic contributions. The test rejected the null hypothesis ($p<1.2\ 10^{-6}$). The post-hoc Wilcoxon Rank Sum tests indicated significant differences between all the groups. The difference between EMCS and controls is barely significant, where the differences among all the other pairs of groups are much more marked (see table 2). The simple value of transfer entropy (first term of the expansion) does not separate the four classes of subjects (fig.3, right).

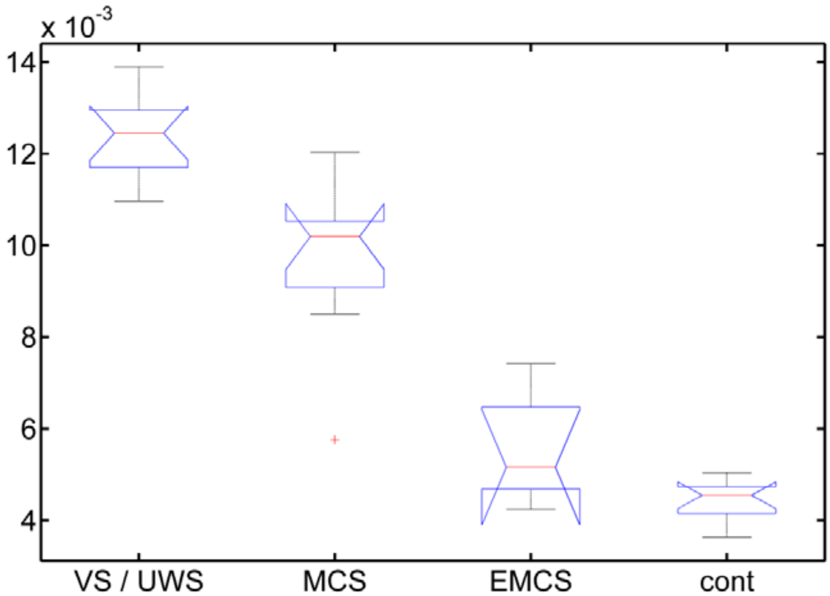


Figure 3: Boxplot of the values of net synergetic contribution (redundancy-synergy) for the four groups of subjects.

VS/UWS-MCS	VS/UWS-EMCS	VS/UWS-controls	MCS-EMCS	MCS-controls	EMCS-controls
p<0.0005	p<0.0005	p<0.0002	p<0.03	p<0.0002	p<0.04

Table 2: p-values of the post-hoc Wilcoxon rank sum test to evaluate differences among the distribution of the overall synergy/redundancy balance for the four groups of subjects.

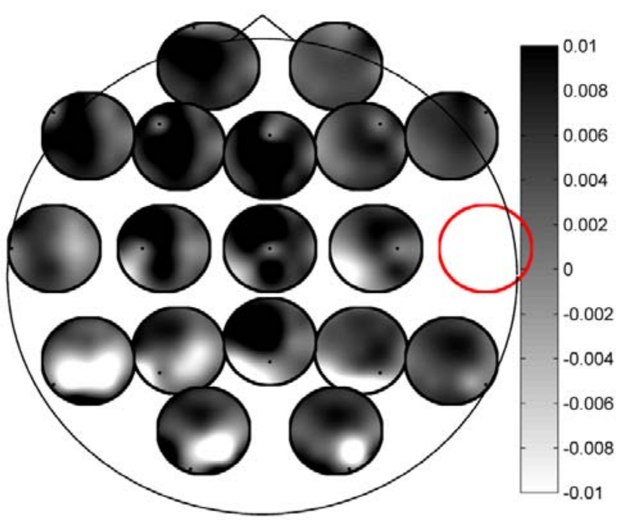


Figure 4: distribution of synergetic duplets (white) and redundant ones (black) for a sample target channel (T8) in healthy subjects.

4. DISCUSSION AND CONCLUSION

A novel framework to analyze interdependencies between electroencephalographic time series recorded on the scalp in terms of directed information transfer was applied to patients with disorders of consciousness. These measures are situated in a general framework to assess the level of consciousness by looking at where and how information is stored and transmitted in the brain, at rest[23,24] or after magnetic stimulation[25].

It was possible to retrieve distinct patterns resulting from the interplay of the dynamics of the nodes of a network and their limited capacity to handle information, given the network structure, and to associate them to the degree of consciousness. The location of bottleneck regions across the scalpcould be interpreted in terms of the different pathways of information transfer observed in controls versus DOC patients and reported in Varotto et al.[26] .That study found that the information transfer increased among the central regions and decreased to and from the lateral regions for DOC patients compared to healthy controls.

Furthermore we have shown that clustering the variables in terms of the shared informational content of their dynamics can disclose information on network function. It is important to underline for example that the difference across states of consciousness is related to the joint contribution of duplets of variables sharing similar informational content, and not to the information transferred between individual nodes.

Further studies aimed to a more subject-specific evaluation or interpretation should include the effect of specific lesions and use controlled reduced consciousness states, such as anesthesia.

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