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Information Communication Networks in Severe Traumatic Brain Injury

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Abstract In this study we explored the use of coherence and Granger causality (GC) to separate patients in minimally conscious state (MCS) from patients with severe neurocognitive disorders (SND) that show signs of awareness. We studied 16 patients, 7 MCS and 9 SND with age between 18 and 49 years. Three minutes of ongoing electroencephalographic (EEG) activity was obtained at rest from 19 standard scalp locations, while subjects were alert but kept their eyes closed. GC was formulated in terms of linear autoregressive models that predict the evolution of several EEG time series, each representing the activity of one channel. The entire network of causally connected brain areas can be summarized as a graph of incompletely connected nodes. The 19 channels were grouped into five gross anatomical regions, frontal, left and right temporal, central, and parieto-occipital, while data analysis was performed separately in each of the five classical EEG frequency bands, namely delta, theta, alpha, beta, and gamma. Our results showed that the SND group consistently formed a larger number of connections compared to the MCS group in all frequency bands. Additionally, the number of connections in the delta band (0.1–4 Hz) between the left temporal and parieto-occipital areas was significantly different ($P < 0.1\%$) in the two groups. Furthermore, in the beta band (12–18 Hz), the input to the frontal areas from all other cortical areas was also significantly different ($P < 0.1\%$) in the two groups. Finally, classification of the subjects into distinct groups using as features the number of connections within and between regions in all frequency bands resulted in 100% classification accuracy of all subjects. The results of this study suggest that analysis of brain connectivity networks based on GC can be a highly accurate approach for classifying subjects affected by severe traumatic brain injury.

Keywords Severe neurocognitive disorder · Minimally conscious state · Vegetative state · Granger causality · Functional connectivity analysis

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Introduction

Traumatic brain injury (TBI) occurs when a sudden trauma damages the brain, disrupts normal brain function, and results in loss of consciousness, posttraumatic amnesia, or neurological findings (http://www.tbindsc.org/). TBI can have profound physical, psychological, cognitive, emotional, and social effects. In the last few years, in an attempt to gain an insight on the changes that normal brain activation undergoes under pathological conditions, brain connectivity analysis has been employed to study activity

synchronization and communication networks in the human brain. Connectivity networks are computed from multichannel neurophysiological activity obtained, for example, via electroencephalography (EEG), which is used to compute coherence and Granger causality (GC) (Granger 1969; Seth 2005; Seth and Edelman 2007) measures between pairs of channels. The former provides information on the extent of synchronization between two time series, while the latter provides a cause-and-effect relationship between the two. More elaborate studies, however, consider interactions among multiple channels simultaneously, an approach that represents more realistic biological interactions.

In this study we set out to quantify any possible differences in brain activation patterns between two subgroups of patients affected by severe TBI (Teasdale and Jennett 1974). More specifically, we attempted to distinguish between patients in minimally conscious state (MCS) and patients with severe neurocognitive disorders (SND) that show signs of awareness (Teasdale and Jennett 1974). To make the comparison more objective, we used several analysis methods, including coherence (Gonzalez and Wintz 1977) and GC computed using existing algorithms (Seth 2005; Seth and Edelman 2007) and a new implementation recently developed by our group that employs least-squares linear regression to model multichannel interactions (Frye et al. 2007a, b).

Materials and Methods

Subjects and Procedure

Details on the participants and the data collection protocol can be found elsewhere (Leon-Carrion et al. 2008). Briefly, 16 patients participated in this study (14 males and 2 females, between 18 and 49 years of age) all affected by TBI, 7 MCS and 9 SND. All patients were screened for drug and alcohol dependency, psychiatric disorders, epilepsy and other neurological disorders before trauma. EEG activity was recorded using a portable device (Truscan32, Deymed Diagnostic, Czech Republic) with 19 electrodes that were placed according to the International 10–20 System, covering frontal, central, parietal, temporal, and occipital regions. Informed consent was obtained from the patients or from their legal guardian according to the approved protocol.

During the recordings, patients were seated in a comfortable chair and asked to remain alert with eyes closed, while they were constantly monitored for signs of drowsiness. Measurements were taken in a softly-lit sound-proof room to avoid any possible distraction. Approximately 3 min of data were collected, with a sampling frequency of 256 Hz and signal bandwidth between 0.1 and 100 Hz. The

data were filtered off-line with a third order Butterworth, bi-directional, zero-phase, bandpass filter between 0.1 and 40 Hz. In four cases, two subjects per group, a highly reliable (Iriarte et al. 2003) Independent Component Analysis (ICA) procedure was used to remove visible artifacts in the recordings caused by ocular movements in frontal electrodes and muscular tension in temporal derivations. A maximum of 2 independent components were selected to represent the artifacts, which were then removed from the original recordings.

Data collection and artifact removal were performed at the Brain Injury Rehabilitation Clinic in Seville, Spain, while all further analyses were performed at the Biomedical Imaging lab in Houston, USA.

Data Analysis

Coherence analysis considers interactions between pairs of channels and it was performed using in-house software (Pophale 2008) written in Matlab (Mathworks Inc., Natick, MA). GC was computed using three different techniques, including the public domain bSMART (Cui et al. 2008) and Seth's GC (SGC) Matlab toolboxes (Seth 2005; Seth and Edelman 2007). The former considers only pair-wise interactions between channels (bivariate regression), while the latter performs a multivariate regression analysis. The third method employed was a newer GC implementation termed Dynamic Autoregressive Neuromagnetic Causal Imaging (DANCI) developed by our group (Frye et al. 2007a, b) originally for magnetoencephalographic activity analysis. DANCI computes separate networks in nonoverlapping frequency bands while adjusting the sampling rate of a signal automatically to improve computational speed (Frye et al. 2007, 2009). In all cases we computed the connectivity networks over five different frequency bands, namely delta (0.1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–18 Hz), and gamma (18–40 Hz) as well as on the full signal bandwidth (0–40 Hz). To simplify data analysis and improve statistical power, the 19 electrode locations were lumped into 5 regions, namely frontal (FP1, FP2, F7, F3, FZ, F4, F8), left temporal (T3, T5), central (C3, CZ, C4), right temporal (T4, T6), and parieto-occipital (P3, PZ, P4, O1, O2).

Coherence Analysis

For every pair of channels, all coherence values in a given frequency band were averaged to obtain a single scalar value for the pair in the entire band, resulting in a 19×19 coherence matrix, for each of the five frequency bands. To obtain only the significant connections, the matrix was thresholded using as optimal threshold the value that maximized the separation between the two groups. The threshold was obtained by exhaustive search for values

between 0.1 and 0.9, in steps of 0.05. Thus, for each subject, a matrix of significant connections was computed.

Then, the five lumped brain regions were considered as the nodes of a graph (Pophale 2008); thus, based on graph theory, we defined a set of 15 connectivity features using the number of significant connection within and across the five brain regions. Finally, for each group we computed an average matrix of significant connections within and across regions. The difference between those two matrices quantified the separation of the MCS and SND groups. Maximization of the difference indicated which threshold was best suited for this study.

Granger Causality

To assess the reliability of the methods in identifying true connectivity networks, we initially performed extensive simulations with synthetic networks whereby the number of nodes and their influence on one another were rigorously controlled (Frye et al. 2009). We explored both small and large networks (up to 50 nodes), each time considering execution time, residual error, and connection strength (Frye et al. 2009).

The actual EEG data were first filtered in five different frequency bands, and then they were normalized to zero mean/unit variance and checked for covariance stationarity following the differentiation approach of Box and Jenkins (Box et al. 2008). For the regression analysis, the optimal model order was obtained using both the Akaike and Bayesian Information Criteria (Frye et al. 2007). An F-statistic on the model residuals was calculated for all methods (Frye et al. 2009). Two values, $P < 0.01$ and $P < 0.05$ (appropriately reduced by Bonferroni correction) were explored to define significance. Additionally, to further limit the number of important connections, we followed an approach that is based on graph theory and is computed as the maximum difference between global and local efficiency in a network of 19 nodes (De Vico Fallani et al. in press). After running 10 simulations of 100 iterations each, the estimated average optimal number of connections was 27. A simulation example for networks of different densities with a maximum of 171 possible connections is shown in Fig. 1.

After constructing a network for each subject and counting only the number of significant connections, the two groups were compared using a t test statistic to identify the areas with statistically significant different connections between the SND and MCS groups.

Subject Classification

To test the capability of the connectivity measures to classify individual subjects correctly as MCS or SND, we
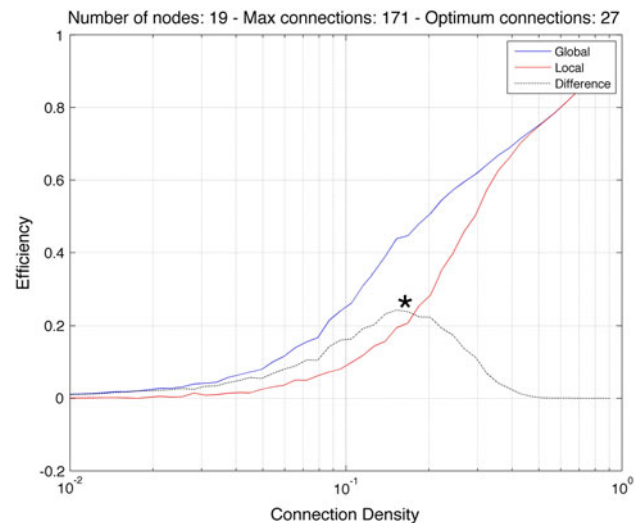

Fig. 1 Selection of the optimum connection density as the maximum differences between the global and local properties of 100 random graphs with 19 nodes

used the number of connections between and within the five brain regions in each frequency band as features with a support vector machine classifier (Cortes and Vapnik 1995). All feature values were normalized between [0, 1]. We only used statistically significant features ($P < 0.05$), as identified by separate t tests. The features were ranked according to t test values. To find the minimum number of features needed, we began with the best feature, and then sequentially we added a new feature and repeated the classification process. This procedure was repeated 100 times on the same classifier.

Results

Simulations

Figure 2 shows a simulation example with a 20-node network, demonstrating that both multivariate GC methods used in this analysis give accurate and fairly similar results. However, in a companion paper (Frye et al. 2009) we showed that DANCI (Frye et al. 2007a, b) had the fastest convergence, smallest residual error, and the best accuracy for a large number of network configurations.

Coherence

The SND group showed a larger number of connections between the various brain areas compared to the MCS group for most threshold values. There are 15 possible combinations of connections within and across the 5 brain areas, and each combination was treated as a feature numbered from 1 to 15, as shown on the x axis of Fig. 3.

Fig. 2 Simulated network with 20 nodes; actual configuration (*left*) and network identified by the SGC (*middle*) and DANCI (*right*) methods
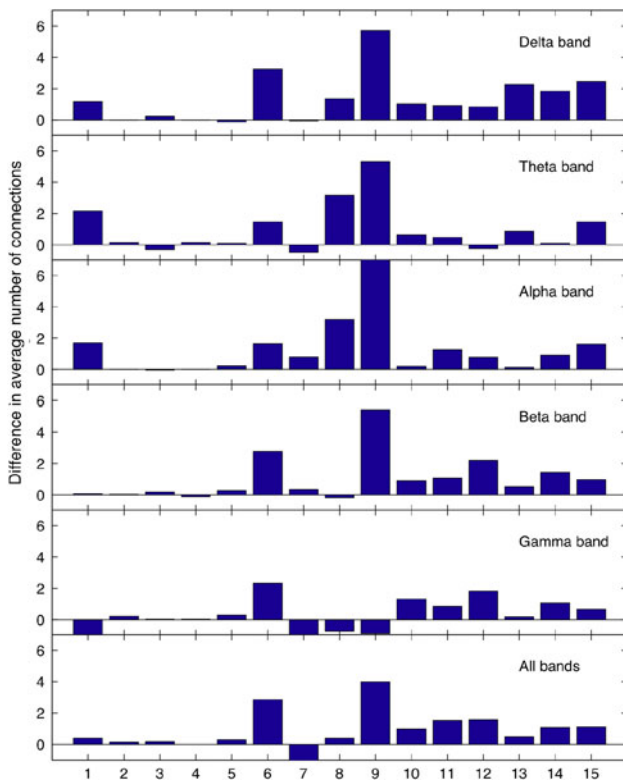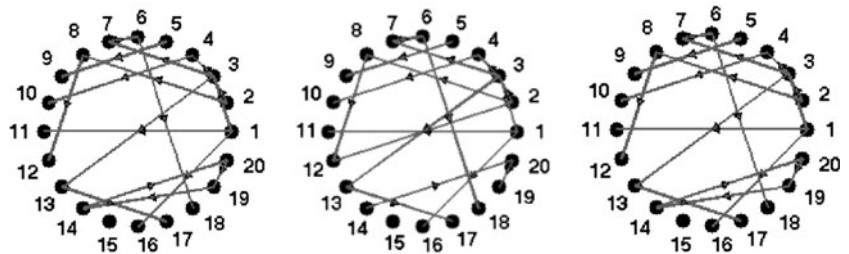

Fig. 3 Differences in average number of connections between the SND and MCS groups at various frequency bands within and across various brain regions for a threshold value of 0.3

Table 1 Percent difference in the number of connections between the SND and MCS groups for various frequency bands and threshold values

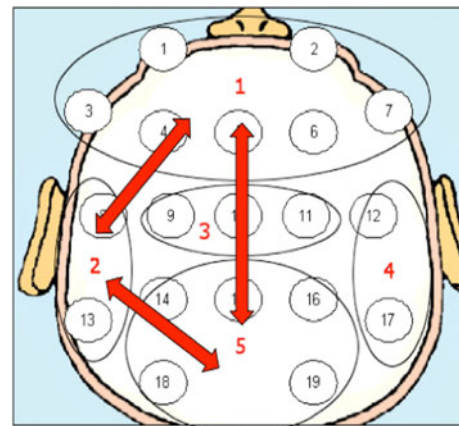| Band	Threshold						
	0.2	**0.3**	0.4	0.5	0.6	0.7	0.8
δ	12.5	**33.3**	17.2	−2.0	−24.1	−66.6	0
θ	17.9	**27.3**	15.6	8.6	3.3	7.7	0
α	21.3	**26.5**	18.6	7.0	31.8	37.5	0
β	6.21	**17.0**	18.6	9.3	23.8	33.3	0
γ	1.8	**0.7**	1.1	−1.75	33.0	28.6	0
All	4.3	**14.7**	10.7	15.9	8.3	0	0

Bold values indicate maximum separation between the MCS and SND groups

Fig. 4 Areas with significant differences in the number of connections between the SND and MCS groups using coherence analysis

The percent difference in the number of connections between the two groups was computed for several threshold values and frequency bands. As Table 1 shows, the maximum separation between the two groups was obtained for a threshold value of 0.3.

Figure 3 shows an example of the difference in the number of connection between the two groups at various frequency bands for all 15 features (possible connection combinations). The features (in decreasing order of significance as ranked by the *t* tests) that produced the maximum separation between the two groups are features # 9, 6, and 12, corresponding to the number of connections between the frontal and parieto-occipital, frontal and left temporal, and left temporal and parieto-occipital regions, respectively, as seen in Fig. 4. The same set of features was statistically significant ($P < 0.05$) at several threshold

values from 0.2 to 0.5, suggesting that the exact value of the threshold does not affect the results appreciably.

Granger Causality

In general, pair-wise bivariate modeling resulted in a very large number of connections within and across most brain regions and did not display any specific pattern in any frequency band. Thus, bivariate analysis was inconclusive. On the other hand, when all regions were tested simultaneously via multivariate modeling, we found significant differences between the two groups that exhibited distinct
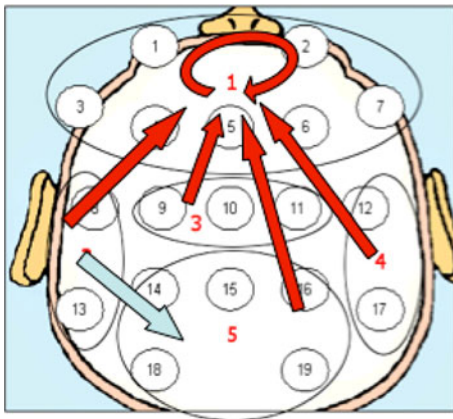
Fig. 5 Areas with significant differences in the number of connections between the SND and MCS groups using GC analysis

patterns. More specifically, at the more strict value of $P < 0.01$, the differences involved only the β band for connections going from all areas to the frontal region, while at the less strict value of $P < 0.05$, an additional connection in the δ band from the left temporal to the parieto-occipital areas became significant, as shown in Fig. 5.

Subject Classification

We found that with 16 features we could get 100% correct classification in all 100 runs, while a subset of the best six uncorrelated features could provide 94% classification accuracy, as shown in Fig. 6.

Discussion

TBI occurs when a sudden trauma damages the brain, disrupts normal brain function, and results in loss of
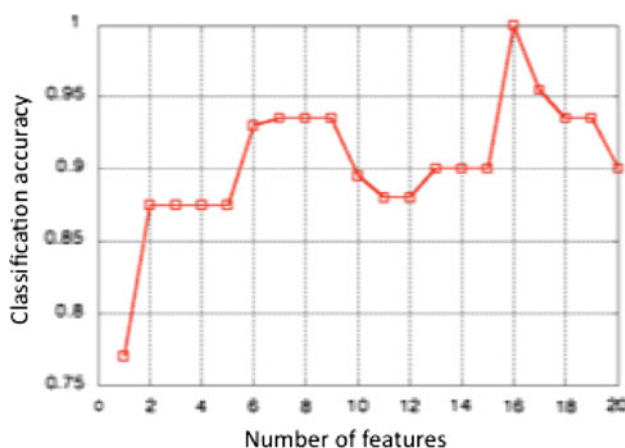

Fig. 6 Subject classification accuracy as a function of the number of features included in the classifier

consciousness, posttraumatic amnesia, or neurological findings (http://www.tbindsc.org/). Often TBI has profound physical, psychological, cognitive, emotional, and social effects. TBI causes substantial disability and mortality: in the United States alone, each year approximately 1.4 million people sustain a TBI, resulting in 50,000 deaths, 85,000 long-term disabilities (Langlois et al. 2006), and an estimated economic burden to society close to $38 billion (Max et al. 1991).

Unfortunately, determining patients' prognosis after TBI and planning for long-term care is difficult and complex (Steyerberg et al. 2008). The most widely used measure of function in rehabilitation is based on assessing the patient's level of independence in mobility, self-care, and cognition. However, it may be an inadequate measure of recovery as it lacks sensitivity in patients with very low or very high levels of function. Therefore, tools to effectively measure outcome and to assess the effectiveness of different treatments are in great need (Robertson and Knight 2008).

MCS and SND are two distinct neuropsychological conditions consequent to TBI: MCS patients are characterized by very limited responsiveness to human interaction, whereas SND subjects exhibit clear evidence of awareness and consciousness. The aim of this study has been to assess whether quantitative methods such as GC and coherence analysis of the EEG can provide, from one hand, a reliable means to classify SND and MCS patients correctly, and from the other, to assess the effectiveness of current treatment and guide patient prognosis. The results obtained in this study show that network analysis provides a set of distinct topological connectivity features that can accurately differentiate the SND from the MCS patients.

From a methodology point of view, both coherence and GC analysis showed that the frontal regions and their connections with the left temporal and parieto-occipital areas formed networks that could differentiate the two patient groups. However, GC provided a network of "higher resolution" by providing also the direction of these interactions/connections. After comparison, we found similarities in the connectivity patterns that were significantly different in the two groups. More specifically, in the higher frequency bands, such as β, the input to the frontal areas from left and right temporal, central, and parieto-occipital regions was of paramount importance, with the SND group forming significantly more such connections than the MCS group. In the lower frequency bands, such as δ, the involvement of left temporal areas and their connection with the parieto-occipital regions was also found significant. Although the GC method requires a higher computational power that spectral coherence, it provides greater details on the connectivity patterns, both in terms of directionality and accuracy. The results of this study agree with our previous findings in normal subjects (De Vico

Fallani et al. in press) in that analysis of brain connectivity based on GC can adequately describe functional properties of complex brain networks and suggest that GC analysis can be a highly accurate approach for classifying subjects affected by severe traumatic brain injury.

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