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Brain Connectivity Networks and fMRI Brain-Computer Interface

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Abstract. The aim of this research activity is to establish a methodological framework, based on data-driven mathematical methods coupled with graph analysis to investigate both functional and effective brain connectivity in fMRI data. This work shows the issues that arise performing the data analysis in frequency domain by using coherence and directed transfer function (DTF).

Keywords: Coherence, DTF, dynamical networks.

1. Introduction

Nowadays the possibility of different recording modalities of brain activity (as in the case of EEG, MEG and fMRI) allows a continuous monitoring of brain activities with high temporal and spatial resolution. Whereas MEG/EEG has high temporal resolution of below 100ms and therefore allow to explore the timing of basic neural processes at the level of cell assemblies, other methods such as fMRI have a high spatial resolution, typically in the order of 2-3 mm, and can record signals from all regions of the brain, unlike EEG/MEG that are biased towards the cortical surface.

The organization, interrelationship and integrated performance of different brain regions are generally described with the term "connectivity" [Friston et al., 1996]. Brain connectivity can be distinguished in structural connectivity, functional connectivity (FC), and effective connectivity (EF). The first refers to the reconstruction of white matter tracts, the second measures the temporal dependence on neural activity patterns of anatomically separated brain regions, while the third considers also the causality or directionality among these patterns.

Starting from functional neuroimaging data, one possible way to examine brain connectivity is to study correlations between signals recorded from different areas. Reaching this aim could be used to establish a methodological framework by coupling signal processing based on data-driven mathematical methods with the graph analysis performed on the connectivity matrix. This integration allows an easy comparison among the connectivity analysis performed through a variety of data driven methods, and can supply a graphic representation and parametric characterization of the brain network [Rubinov et al., 2010]. Graph theory becomes the natural framework for the exact mathematical representation of brain complex networks [Bullmore et al., 2009].

The developments in the coupling of signal processing and the theory of complex networks have motivated several studies that have successfully used EEG/MEG [Stam, 2010] and recently fMRI [Goebel et al., 2003; Van Den Heuvel et al., 2010] to investigate state-dependent alterations in topological properties of networks due to pathological conditions.

In the literature different data driven linear methods are presented to define the level of both functional [Miltner et al., 1999; Zhou et al., 2010] and effective [He et al., 2011] connectivity among brain areas in time or frequency domain. Furthermore some examples based on nonlinear time series analysis are included [Di Grazia et al. 2009; Stam, 2010].

In this paper as proof of concept a study based on FC and EC coupled with graph analysis on fMRI datasets recorded during a Brain-Computer Interface (BCI) protocol [Weiskopf et al., 2004] is presented. In particular the FC has been based on coherence, while the effective connectivity has been

evaluated using the multivariate autoregressive (MVAR) model in the frequency domain, referred as directed transfer function (DTF) [Kaminski et al., 2001].

The identification of the frequency values leading to a greater variability in the construction of brain networks plays a fundamental role for the establishment of an automatic procedure, as discussed in previous works in which approaches based on statistics and surrogate data analysis have been proposed [Faes et al., 2004]. In this paper the statistical analysis of the connectivity matrices has been coupled with physiological hypotheses to investigate the possibility of identifying a direct measure that could drive these choices.

2. Material and Methods

2.1. Case Study

In this fMRI Brain-Computer-Interface protocol subjects were trained to regulate pain evoked activity performing a specific task. Subjects received painful transcutaneous stimuli to the base of the 4^{th} digit of the right hand using a small concentric bipolar needle electrode. The electrical pulses were applied using a digitimer DS7A constant current electrical stimulator. Pulses lasted 2 ms and were given with a 2 Hz rate. The stimulation strength was individually determined to be at 70% between pain and tolerance threshold. The brain response to the painful stimulation was recorded and analyzed in real time during the stimulation. The mean signal change in specific regions of interest (ROIs) was computed, subtracted (according to the condition) and feedback to the subject was provided in the form of a moving ball.

The goal for the subject was to move the ball on a screen in the direction of an arrow next to the ball (up or down). Subjects did not receive specific instructions as to how to select a strategy for moving the ball, i.e. influencing activity in the ROIs. For the feedback signal computation two ROIs were selected, coding for different aspects of pain perception: *Anterior Cingulate Gyrus* (ACC), related to the affective aspect of pain and *Left Posterior Insula* (pInsL), related to the sensory aspect of pain [Schnitzler & Ploner, 2000; Peyron et al., 2000; Peltz et al., 2011].

The feedback was computed by subtracting mean signal changes in the two pain relevant ROIs (the ACC and pInsL) from one another, thus feeding back the difference in activation in response to the stimulus. In terms of feedback computation for learning the task, two conditions are assumed. The first, referred as INS_U, entails that the ball moves up when activity in pInsL is greater than in ACC (pInsL>ACC), while in the other case, referred as INS_D, the ball moves down when activity in pInsL is smaller than in ACC (pInsL<ACC).

The study consisted of a baseline session in the presence of the stimulus but without a moving feedback or attempts to change pain sensation and one week later of four consecutive days of practice. In both cases a practice run consisted of 285 full scans (7.125 min, considering that each scan is 1.5 s long, thus the sampling frequency is 0.66 Hz): 6 ON blocks (30 scans- 45 s) during which painful stimulation (electroshock) occurred and 7 OFF blocks (15 scans- 22,5 s) during which subjects performed mental arithmetic. The two feedback conditions were randomly presented, in a way that each condition was practiced 6 times.

In this paper one subject fMRI data for the INS_U condition on all trials was analysed. The following analyses are based on the extracted signal change of the offline pre-processed times-series of 9 ROIs, including an unrelated ROI in which the signal change was expected to be independent from the pain stimulation.

All the other 8 ROIs were all selected for their involvement with pain processing and were identified by an offline GLM analysis of all single training fMRI datasets per condition using BrainVoyager QX 2.3 (Brain Innovation, Maastricht, The Netherlands; Goebel, 2001). The additional ROIs included the left anterior insula (aInsL), the left and right secondary somatosensory cortices (SII_L, SII_R), the medial cingulate gyrus (MCC), the left primary somatosensory cortex (SI_L), and the right posterior insula (pInsR).

2.2. Connectivity Analysis

The recording modality (fMRI) involves a number of specific issues to be faced during data preparation, pre-procesessing, and analysis. The first phase (data preparation) leaves several options like varying recording modalities and protocol conditions and expectation (e.g. from selection of the ROI to the time windows and sampling rate). The second phase (data pre-processing) requires the

frequency and the statistical analysis. A better understanding of the data under-observation can lead to an informed choice of the connectivity analysis method and to a better interpretation of the results. The third phase (brain connectivity) focuses on the functional and effective connectivity analyses.

In this paper the FC has been evaluated using coherency analysis while for EC the directed transfer function (DTF) was used. Both methods allow calculating the connectivity matrix (CM), in which the level of functional connectivity between two areas (i,j) is computed as a measure of the linear independence between the time-series of the two brain regions in the frequency domain.

To investigate brain connectivity we focused our attention on the sensitivity to the connectivity activity in specific frequency bands. By plotting the connectivity dynamics for all the pairs of ROIs (i,j) versus the frequency (see Fig. 1, on the top) those changes are made visible. These connectivity dynamics for all the ROI-pairs presents a higher level of variability, and it is not easy to classify ROI-pairs changes by visual inspection. The frequency value that leads the maximum for each ROI(i,j) trend and the variation coefficient (VC) among all ROIs(i,j) for each frequency was calculated to quantify this variability (see Fig. 2, in the middle) and select the frequency values that could be of interest (peaks or plateau).

The fourth phase (threshold definition) assesses the existence of a functional connection by using a predefined cut-off threshold (un-weighted approach) or by defining a connection strength value (weighted approach). In the first case, the establishment of an automatic procedure to determine a suitable threshold and then derive an un-weighted graph that could have a physiological relevance at a higher level would be useful.

For this purpose during the case study establishment an unrelated ROI was selected. The desired threshold (named adaptive threshold) was set to be the minimum value at which the unrelated ROI was disconnected from the graph. The threshold has been established starting from statistical analysis on the histogram of the CM, for previously fixed frequency values (see Fig. 2 on the bottom). The result is a graph in which nodes can be defined as fMRI ROIs. If the value of the adaptive threshold (AT) leads to a significant number of connections (NC) or in weighted graphs, further examination of its organization might be necessary to use graph theory metrics.

Coherence

The simplest method for estimating functional connectivity in the frequency domain is coherence analysis. The coherence $Coh_{ij}(f)$ between any two individual time-series (y_i, y_j) at frequency f is defined as the normalized cross spectral density between (y_i, y_j). The squared coefficient of coherence can be interpreted as the proportion of the power in one of the two time-series (at a selected frequency), which can be explained by its linear regression to the other time course.

Coherence is a positive function bounded by 0 and 1 and it is symmetric in i and j (the graph is undirected). A measure of coherence, such as an average over a frequency band, is capable of detecting zero time lag synchronization and fixed time nonzero time lag synchronization, which may occur when there is a significant delay between two neuronal population sites. However, it does not provide any information on directionality of the coupling between the two recording sites.

Directed Transfer Function

Granger causality is a measure that attempts to extract and quantify the directionality from brain signals. It is based on bivariate autoregressive (AR) estimates of the data, calculated from pairwise combinations of sites. A time series y_i is said to Granger-cause y_j if it provides predictive information about a future value of y_j. MVAR model estimation is one method to measure this.

The algorithm adopted for the model order identification (p) was ARFIT [Schneider et al., 2001], which produces estimates of the parameters of an MVAR model. To optimize the model identification, the Akaike final prediction error was chosen. The MVAR order indentified for trials (1,3,4,5) was p=2 and for trials (2,6) was p=3.

The DTF model is the transfer function that can be derived for each pair of ROIs resulting in a fixed frequency making it possible to estimate a connectivity matrix, where each element weights the mutual influence between two ROIs. The connectivity matrix is not symmetric, carrying information about the directionality of brain area communication.

The frequency range considered is [0.06 – 0.33] Hz with a step of 0.01Hz. The maximum value was assumed equal to half of the sample frequency for the Nyquist criterion. The minimum value was set to avoid the examination of the connectivity outside the trial range.

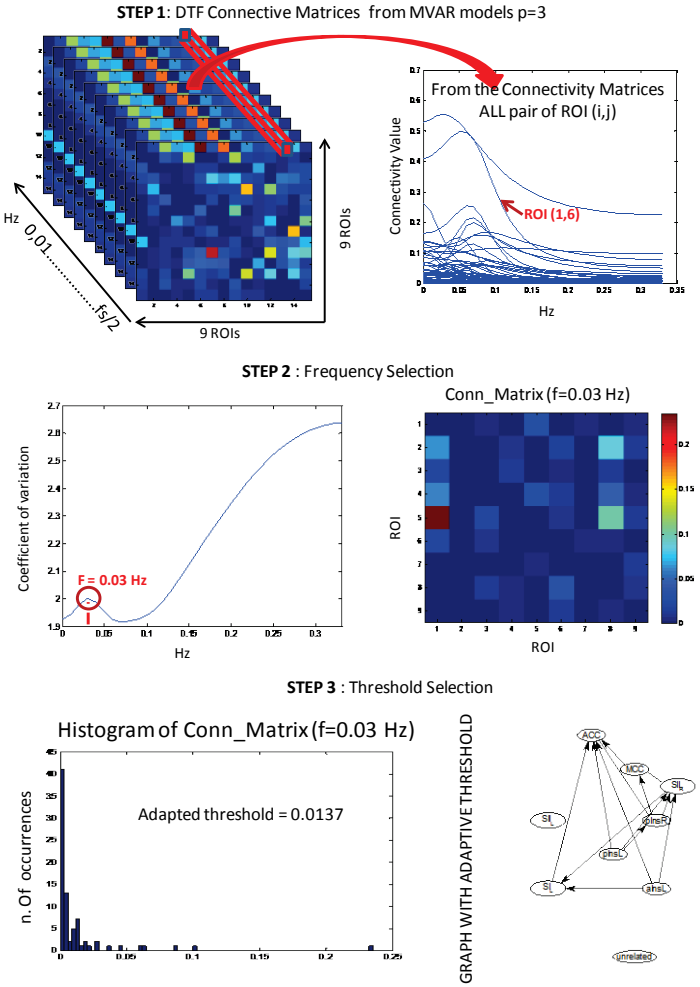

Figure 1. *An Example based on the EC on trial 1. (top) CMs and trends of all pairs of ROIs (i,j) versus frequency; (middle) the VC trend and the CM selected for (f=0.03Hz), (bottom) histogram of the CM and brain network obtained for the adaptive threshold.*

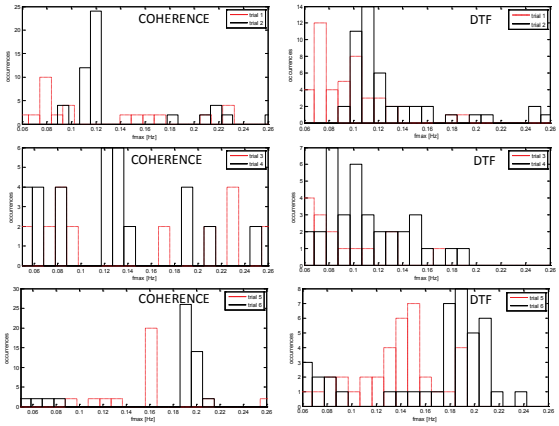

Figure 2. *Histograms related to the occurrence of each frequency as dominant in the ROI(i,j) trend for all trials. (left column) calculated from the coherency, (right column) calculated from the DTF.*

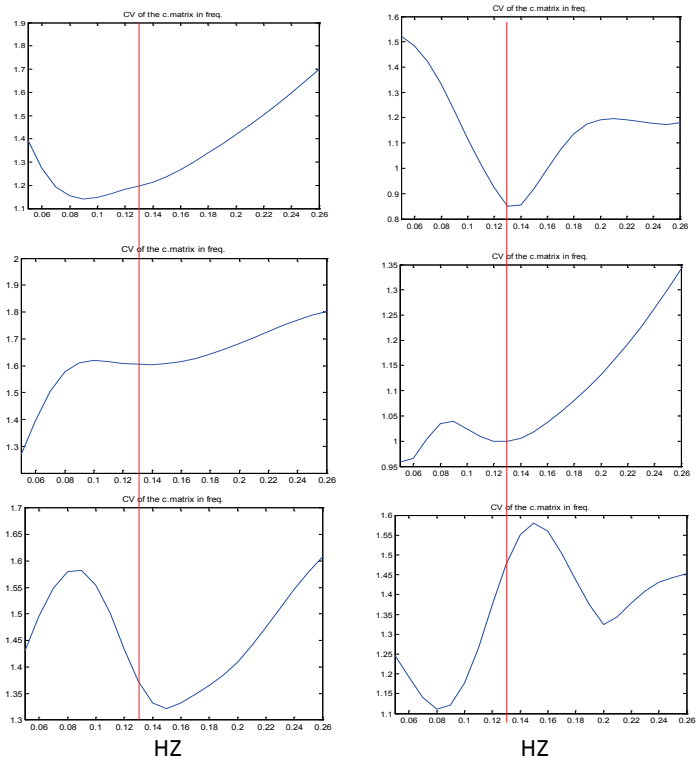

Figure 3. *Trends of the VC versus frequency calculated from the DTF CMs for all trials.*

3. Results

The histograms related to the occurrence of each frequency as dominant in the ROI(i,j) trend calculated from the coherency (left column) and DTF (right column) are shown in Fig. 2. The histogram for trials (1-2) are in the first row, trials (3-4) in the second and trials (5-6) in the third. Trials (1-3-5) are in red whereas trials (2-4-6) are in black.

Noticeably for both methods the distribution seems to be Gaussian above all in the first and last trial pairs, while the distribution in trials (3-4) becomes uniform and no specific peak can be distinguished.

In addition it is possible to observe that the peak values move from a lower band (B1=0,06-0,12 Hz) in trials (1-2) to a higher band (B2=0,13-0,2 Hz) in trials (5-6).

Despite this similarity the VC evaluated by the coherency shows a higher variability than the one of the DTF. In Fig.3 the trends of the VC evaluated by DTF CMs versus frequency for all the trials are reported.

Consistent with the frequency analysis, the sensitivity to both trials and indentified frequency bands could be enhanced. The vertical line splits the frequency range in the bands (B1 and B2). In particular it can be noticed that the peak in the frequency distribution is mainly related to the minimum in the CV trends.

The consideration related to the frequency analysis and to variation coefficient trend allows for the selection of the connectivity matrix with a greater level of pattern variability. The CMs were averaged over the two identified bands to perform the adaptive threshold (AT) selection phase.

In the first and second row of Fig.4 for the two bands respectively, the AT values (blue line) and the related number of connections (black line) obtained through both coherence (first column) and DTF (second column) analyses versus trial are reported. It is possible to notice that the result sensitivity is higher.

For the coherency the number of connections (NC) decreases in B1 and increases in B2, at the same time the AT increases in B1 and shows a saddle point in trials (3-4) in B2. Similarly for the DTF the NC decreases in the B1, but a saddle point is in trials 4-5 in B2. On the other hand AT trends are the same in B1 and B2 showing a sudden change respectively in trail 3 and trial 4. This behavior can be distinguished also for coherence AT in B2.

In Fig. 5 the brain networks obtained through both coherence and DTF are reported. In the case of AT we get a higher number of connections. For easy visual comparison of the obtained graphs, a constraint was set limiting the maximum number of connections to be shown to 4 (respectively 90th

and 95th percentile of the CMs values).

It is not easy to compare the networks, considering only one subject/condition results, but it is noticeable that paths are mainly conservative being restricted to similar pathways, involving mainly (PINS_L, PINS_R, ACC, MCC). The trial changes seem to be very sensitive to both the frequency range and the used method.

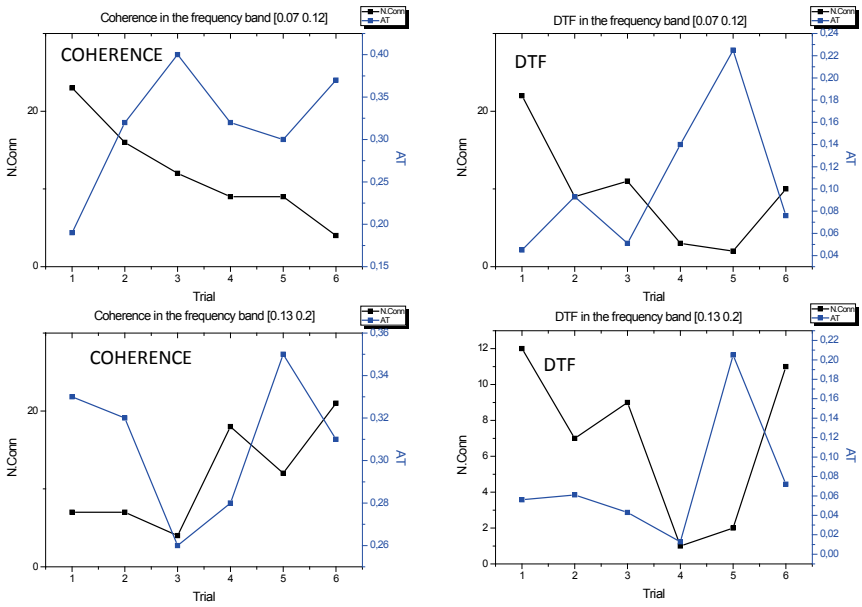

Figure 4. *. AT values (blue line) and NCs (black line) for coherence and DTF versus trial: (top) in B1 and (bottom) in B2.*

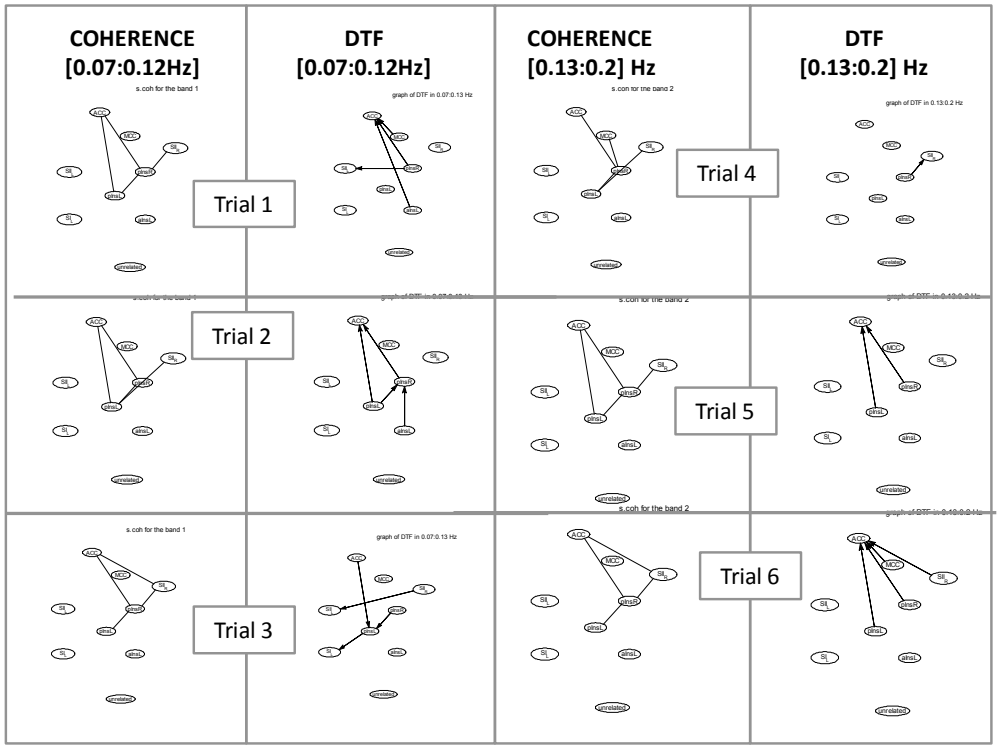

Figure 5. *Brain Network calculated by coherence (at 90th percentile) and by DTF (95th percentile) for each trial and band*

4. Conclusions

Despite the proliferation of mathematical methods and many case studies, there is no general consensus on the most accurate and efficient way to analyse brain activity. This research is focused on the establishment of a general framework for studying the nature of interactions between brain areas, by integrating different analysis approaches and procedures that can provide an automatic analysis within the same platform.

The results obtained by the fMRI case study presented here considered two analysis approaches, both in the frequency domain, one based on functional connectivity and the other on effective connectivity. This allows a glimpse on the potential of this tool to establish strategies to investigate functional neuroimaging data in the light of different research questions using the same dataset. The comparison of the graphs related to the brain networks clearly highlights the sensitivity of the results dependent on the frequency and the analysis method.

The integration of the graph theory and statistical parameters together with the classical connectivity analysis seems to be a promising approach, but at the same time these results increase the need for a further optimization of the procedure for the frequency and the threshold selection for a deeper understanding of its relation with the process under investigation.

Traditional analyses of fMRI data focus on differences in the signal strength variation, i.e. the height of activation in specific brain areas and the exact localization of the activity. In the case of neurofeedback protocols, such as the one highlighted here, this information is only partially of interest since involved regions have to be identified beforehand. Important differences in frequency related changes of activity due to learning or as a difference between subjects could reveal mechanisms of a training effect and regulation capacity that are otherwise overlooked. These frequency related analyses are not exploited in fMRI data so far, in part because of poor sampling rates above 2.5s per scan. With this barrier broken these methods will have a valuable significance in the neuroscience field by supplying a data analysis tool to be used both for the study of neuronal and cognitive processes and, for a better interpretation of fMRI compared to MEG/EEG data.

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