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Functional Neuro-Imaging and Brain Networks

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Abstract. The aim of this research was to establish a methodological framework, based on data-driven identification methods coupled with both graph analysis and statistics to investigate the functional and effective brain connectivity in neuroimaging data recorded from different modalities. As proof of concept functional and effective connectivity coupled with graph analysis is presented on fMRI datasets recorded during a Brain-Computer Interface (BCI) protocol. Particularly the functional analysis has been based on coherence, while effective connectivity has been evaluated using the multivariate autoregressive model (MVAR) in the frequency domain, referred to as directed transfer function (DTF). An automatic procedure to investigate the frequency values leading to a greater variability in the construction of brain networks based on the statistical analysis of the connectivity matrices has been investigated. The comparison of the graphs related to the brain networks highlights clearly the sensitivity of the results to the frequency and the analysis method, underlining the need and the potential of the proposed approach.

Keywords: Brain Connectivity, fMRI data, graph analysis, signal processing, data driven methods.

1. Introduction

Functional neuroimaging is a multidisciplinary research field that encompasses techniques devoted to a better understanding of the human brain at a higher level, using imaging techniques such as electroencephalography (EEG) or magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI). 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 (EC). 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 for an easy comparison among the connectivity analyses performed through a variety of data driven methods, and can supply a graphic representation and parametric characterization of the brain network. Graph theory becomes the natural framework for the exact mathematical representation of brain complex networks [Bullmore et al., 2009; Rubinov et al., 2010].

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 fMRI [Van Den Heuvel 2010] to investigate state-dependent alterations in topological properties of the networks due to pathological conditions. In the literature different data driven methods are presented defining the level of connectivity among brain areas, comprising linear methods based on time-lag correlation and coherence [Miltner et al., 1999], as well as the multivariate autoregressive model in the time [Goebel et al., 2003] or frequency domain [Kaminski et al., 2001]. Furthermore some examples based on

nonlinear time series analyses are included [Di Grazia et al., 2009].

Despite the proliferation of mathematical methods, toolboxes [Zhou et al., 2009; He et al. 2011] and many case studies, there is no general consensus on the most accurate and efficient way to analyze this type of brain activity. This research is focused on the establishment of a general framework for studying the nature of interactions between brain areas. It can have a valuable significance in the neuroscience field by supplying a tool for data analyses to be used both for the study of neurological and cognitive processes and for a better interpretation of fMRI compared to MEG/EEG.

During the establishment of this platform several issues have arisen regarding the analysis method, the graph generation and the coupling between them.

In this paper a proof of concept of functional and effective connectivity coupled with graph analysis is presented derived from fMRI datasets recorded during a Brain-Computer Interface (BCI) protocol [Weiskopf et al., 2004]. In particular the functional analysis has been based on coherence, while the effective connectivity has been evaluated using the MVAR model in the frequency domain, referred to as directed transfer function (DTF).

The main effort has been the establishment of an automatic procedure based on the statistical analysis of the connectivity matrices in order to investigate the frequency values leading to a greater variability in the construction of brain networks. The procedure has been based on the results obtained from the DTF analysis that leads to a lesser variability than the results from the coherence analysis.

The comparison of the graphs related to the brain networks will highlight the significance and the potential of the proposed approach.

2. Material and Methods

2.1. An fMRI based 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, the assumed condition entails that the ball moves down when activity in ACC is greater than in pInsL (ACC>pInsL).

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 fMRI data of a subsample of four subjects out of ten was analysed. The four subjects selected had a consistently correct response to the feedback in at least 4 of the 6 training runs and showed an improvement from trial 1 to trial 6. The following analyses are based on the extracted signal change of the offline pre-processed times-series of 8 ROIs.

These 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. Brain Connectivity Analysis

The block diagram that presents all the analysis phases (coloured in blue) and the results in terms of data, and the connectivity matrix (CM) or graph (coloured in grey) that were considered is reported in Fig.1. In this context the *brain connectivity* study has been focused on both the functional and effective connectivity analyses. The coherence function was calculated for the evaluation of the functional connectivity while the directed transfer function (DTF) was used for the effective connectivity. Both methods allow to calculate 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, as highlighted in the red block below in Fig.1, by defining a strategy for the identification of frequency ranges or bands of interest.

The analyses were performed in selected frequency ranges and a single connectivity matrix was extracted for each of those ranges. Following the *threshold definition* phase, the existence of a functional connection was assessed by using either a predefined cut-off threshold (un-weighted approach) or by defining a connection strength value (weighted approach).

In the case of an un-weighted graph, the nodes can be defined as fMRI ROIs, connections between ROI pairs are established if the respective value of the CM weight is above an established threshold, otherwise the ROIs remain unconnected.

For the un-weighted approach the establishment of an automatic procedure to determine a suitable threshold (second red block in Fig. 1) and then to derive an un-weighted graph that could have a physiological relevance at a higher level, would be useful. This procedure is under study and some results have been already presented in [Bucolo et al., 2012].

In this paper thresholds for un-weighted graphs were determined by statistical analysis of the histogram of the CM for previously fixed frequency ranges, generating the binary CMs.

Finally, the inference among the binary connectivity matrices obtained from each subject was made in the attempt to identify a single graph representative of the trials and the baseline in each frequency band selected.

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. For all the subjects and trials, the MVAR order indentified was in the range of p=2 up to p=4.

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 (see Fig.2(a)).

Frequency Selection

By plotting the connectivity dynamics for all the pairs of ROIs (i,j) versus the frequency it is possible to highlight the variability in the frequency range (see Fig.2(b)). These connectivity dynamics for all the ROI-pairs present a higher level of variability, and it is not easy to classify ROI-pair changes by visual inspection. As expected, the variability of the coherence analysis is higher than the variability in the DTF analysis. In Fig.2 (c) histograms related to the occurrence of each frequency as dominant in the connectivity trends of ROIs(i,j) are shown.

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 considering the DTF analysis were calculated to quantify this variability (see Fig. 3).

By visual inspection of the histograms it was possible to conclude that the frequency ranges of interest can be identified as the maxima and minima of the VC curve. Each point is an index of the frequency by frequency internal variability of the CM taking into account simultaneously the strength of the connectivity of all the ROI pairs.

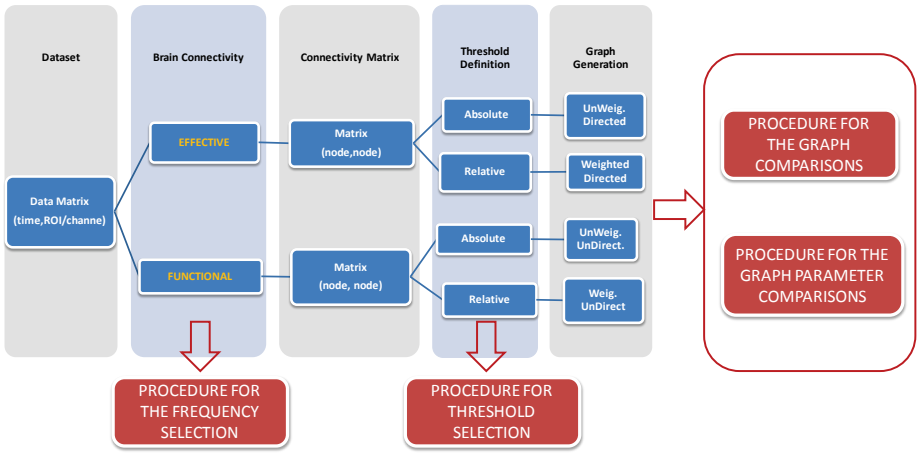

Figure 1. *Analysis Framework Flow Diagram.*

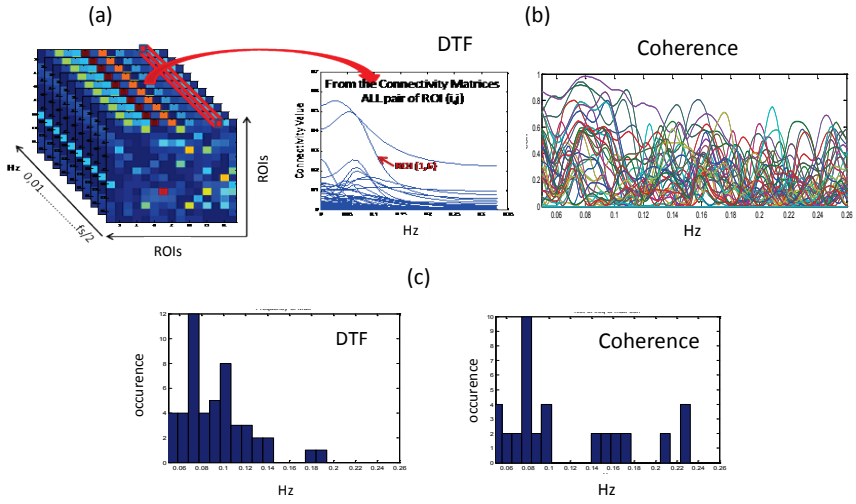

Figure 2. *An Example of frequency varibility. (a) Representation of the CMs spaced across the considered frequency range [0.06 – 0.33] Hz with a 0.01Hz step. (b) Connectivity dynamics for all the pairs of ROIs(i,j) versus the frequency, on the left for the DTF analysis and on the right for the coherence. (c) Histograms related to the occurrence of each frequency as dominant in the connectivity trends ROIs(i,j).*

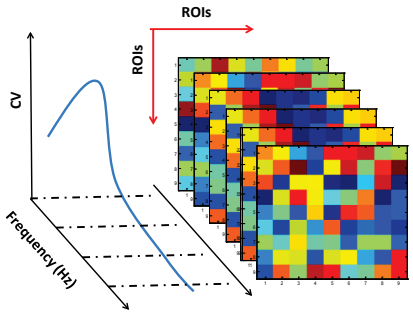

Figure 3. *Chart of the frequency association between the CMs and the Variation Coefficient curve.*

3. Results

The results obtained for the frequency selection calculated from the DTF analysis are shown in Fig.4. The histograms related to the maxima and the minima of the VC curve for all subjects and all trials are reported at the top and in the middle, while the histogram related to the occurrence of each frequency as dominant in the ROI(i,j) trend is at the bottom. Note that the peak values of the first couple of histograms emphasize the frequency trend of the last histogram.
The frequency bands selected were (B1=0.035-0.045 Hz), (B2=0.085-0.095 Hz), (B3=0.135-0.16 Hz) and (B4=0.223-0.243 Hz).

Consistent with the frequency analysis, the sensitivity to both trial 1 (first trial) and trial 6 (last trial) at indentified frequency bands could be enhanced by the graph analysis.

In Fig. 5 the statistics among subjects (mean and standard deviation) on the threshold values obtained assuming a percentile equal to the 70^{th} for the extraction of the strongest connections in the CMs are reported. The plot on the left refers to the coherence analysis while the one on the right to the DTF analysis, in both cases the statistics are computed considering the four frequency bands and both trials (1 and 6).

The threshold value identified is always smaller in trial 6 than in trial 1 for both methods and all bands. The decrease of the threshold value with the increase of the frequency can be inferred from the lower values of the weights in the CM at low frequencies, otherwise the decrease in the magnitude of the standard deviations in trial 6 compared to trial 1 for all bands suggests less variability in the threshold in the case of trained subjects. This result could be useful in the establishment of a procedure for threshold selection.

In Fig. 6 the brain networks obtained through both coherence (red line) and DTF (black line) are reported. To focus the attention on the strongest connection, the graphs are generated using a threshold value equal to the 70^{th} percentile of the CMs values. For each CM in the coherence analysis, the 8 strongest connections out of 28 are extracted (in this case the CM is symmetric), while in the DTF analysis we obtained 17 out of 56 connections. Common network structures among all subjects were then identified for the baseline (fist column), and the first (trial 1, second column) and the last practice (trial 6, third column).

Comparing the graph obtained for the coherence analysis, it is evident that the (pInsR-pInsL) connection is present in all trials of B1 and B3. The connection (SII_R-SII_L) instead is present for B1 (baseline) and B2 (baseline and trial 1). No connections are found for B2 (trial 6) and B4 (trial 1- trial 6). This analysis does not allow a distinction between the network pattern before and after the exercise practice.

A different perspective is opened from the DTF analysis. Considering each band no connection is presented at the same time on the baseline and on both trials.

There are no connections on the baseline (B1 and B2) and trial 1(B2) and just one connection on trial 1 (B1). However on trial 6 for both bands (B1 and B2) a specific net can be identified consisting of two links, (aInsL-SII_L) and (SI_R-SII_L). When considering B2 this pattern is complemented by two more links. On trial 6 (B3 and B4), this network structure is not present.

Further, for B3 and B4 no common connections are visible on the baseline. Differently from the previous bands, the connections on the baseline and on trial 1 increase and the connections on trial 6 decrease. It is peculiar to observe that only one connection is present in both cases and involves always as a starting node pInsL with the destination node changing from aInsL in B3 to pInsR in B4.

The last row of the table in Fig. 6 shows the graphs obtained when the same analysis is performed considering the whole frequency range (0.035-0.243 Hz). The network architectures identified are in all cases the same of B1. The reason for this overlap can be that the values of the weights in the CM are higher at low frequencies (see Fig.2(b)), rendering this behavior the dominant one.

The results obtained show that only the DTF analysis allows for a distinction between the brain activity before and after the neurofeedback training, while the coherence seems to be able to capture some more general characteristics. Furthermore, it is evident that the frequency can play an important role in these studies.

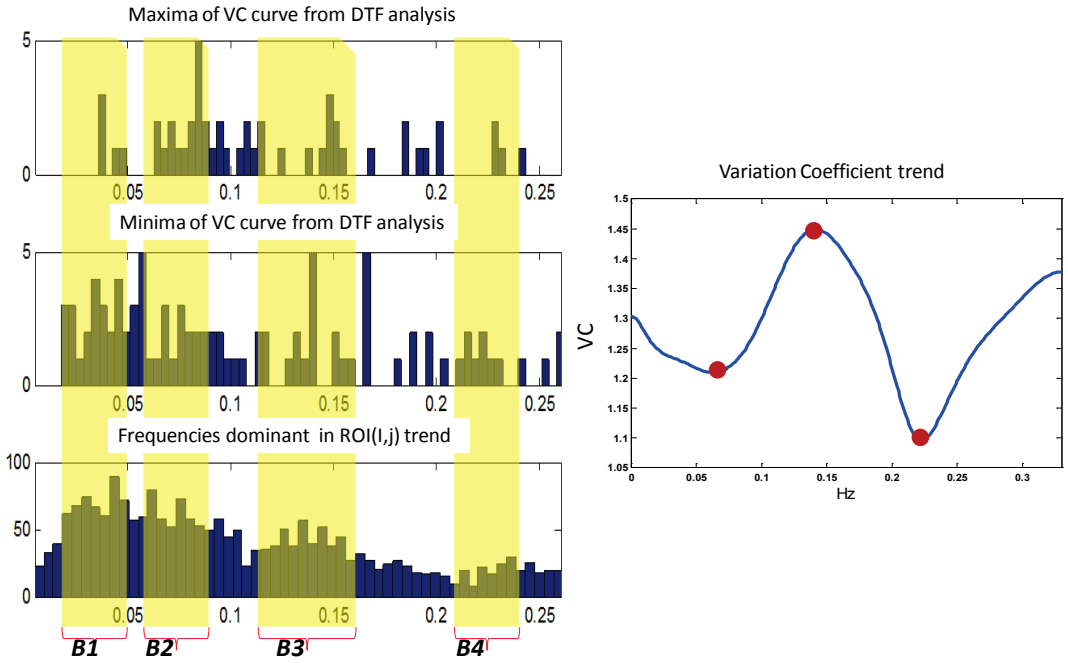

Figure 4. *. Frequency band selection calculated from the DTF analysis. (on the left) Histograms related to the maxima (on the top) and the minima (in the middle) of the VC curve for all subjects and all trials, at the bottom the histogram related to the occurrence of each frequency as dominant in the ROI(i,j) trend. The four frequency band selected are highligthed (B1,B2,B3,B4).(on the right) VC curve for the subject 5 in trial 1.*

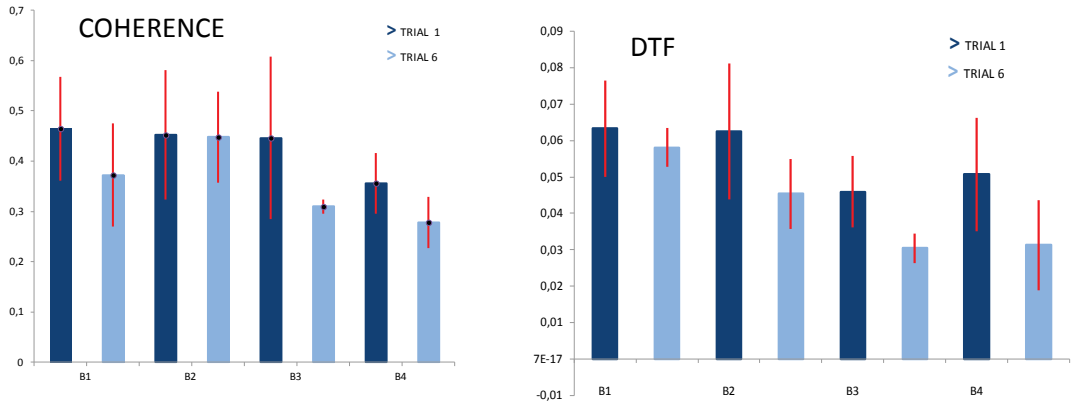

Figure 5. *Statistics (mean and standard deviation) among subjects on the threshold values obtained assuming a percentile equal to the 70th for the extraction of the strongest connections in the CMs. The results are reported for coherence (on the left) and DTF (on the right), considering the four frequency bands selected and both trials (1 and 6).*

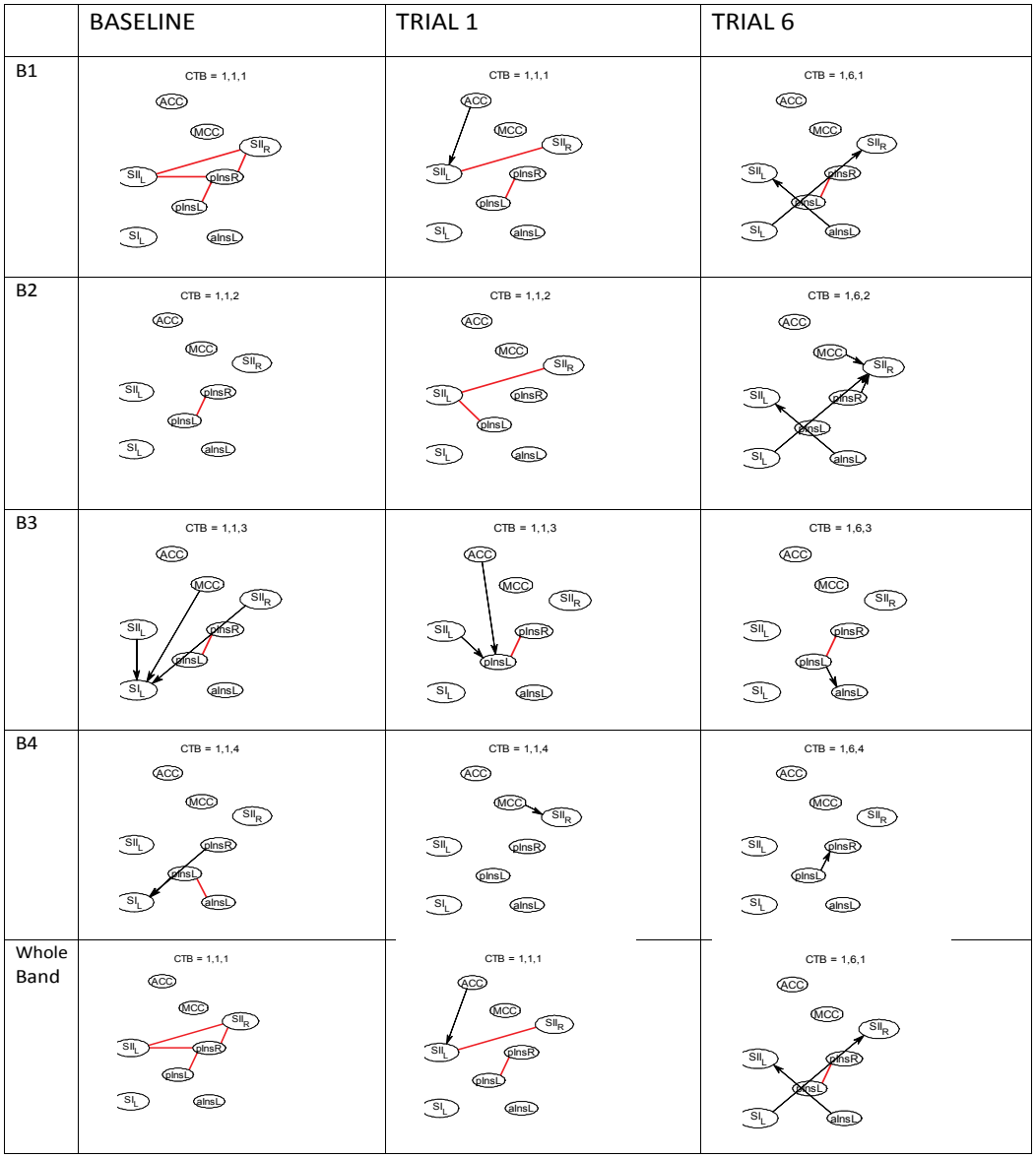

Figure 6. *Brain networks in common among all subjects obtained through both coherence (red line) and DTF (black line) for the baseline (only pain stimulation) and both the first (trial 1) and the last exercise practice (trial 6).*

4. Conclusions

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.

At the same time there is a proliferation of mathematical methods and many case studies on the analysis of these brain data, but no general consensus on the most accurate and efficient way to analyze 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.

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. In our example we saw a shift in network patterns from trial 1 to trial 6 both in FC and in EC exceeding in- or decreases in signal change. These frequencies 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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