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Brain network study during resting states

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Abstract

The application of network science and graph theory in neuroscience has flourished recently. This relatively new field of research, usually referred to as network neuroscience, gave great contributions in the understanding of how human cognitive functions are linked to neuronal network structure, providing a conceptual frame that can help in reducing the analytical brain complexity and in modeling the topological structure of brain functions (especially interesting in comparisons between normal and pathological cases), under various conditions of brain activity. In this work, we focus on the analysis of EEG functional connectivity in one subject during resting state, through a comparison between his functional connectivity in closed and open eyes resting.

Introduction

Brain networks can be studied in two different states: an active state and a resting state. Once treated, they allow us to draw connectivity graphs. These graphs are used to analyze the nervous system in macro and micro scales. The first real studies began in the 19th century. The number of Brain networks analyses is increasing. Thanks to new images acquisition methods, these studies are more feasible. These studies are used in treatments and researches about neurological diseases, and also to delve deeper in understanding how brain areas are connected when the subject under analysis is performing some specific actions. In this project, we are going to use two time series related to EEG captures of 1 minute on 64 brain areas: **S064R01** and **S064R02** (respectively referring to Eyes-Open and Eyes-Closed EEG captures in resting state of the same subject). An extended network analysis on both captures will be conducted, in order to compare the main connectivity features of the channels captured during EEG in both states. This will lead to conclusions about the main active connections between brain areas during resting state, and which of them remain active or are deactivated when eyes are open or closed.

Methods and Results

Connectivity

In order to obtain the networks which represent eyes-opened and eyes-closed conditions, we need to estimate functional brain connectivity among 64 channels using MVAR estimators such as Partial Directed Coherence (**PDC**) or Direct Transfer Function (**DTF**). To build a binary network we used two different techniques, first we use different thresholds on the density value of the obtained network. Second, we apply a statistical validation method (more precisely a resampling procedure using the python library SCot) to filter out the values which are not significantly different from zero (**p-value ≤ 5%**). In both cases we cut off the functional brain connectivity values between a channel with itself.

In ***Figure 1*** we put the binary adjacency matrices(**both estimators**) obtained using the first technique(threshold on density=20%, chosen relevant frequency=10Hz - alpha rhythm). We notice the main difference for the two estimators in both conditions(eyes-opened and eyes-closed) are in channels(29,30,31,32,33). In EO they have a lot of connections with channels(from 40 to 64) but in EC condition we have less connection between these groups of channels(we can see this pattern also with other density) . In ***Figure 2*** we put the binary adjacency matrices(**DTF estimator**) obtained from the variation of the threshold on density value(1%, 5%, 10%, 20%, 30%, 50%) to see their behaviour. We noticed that of course by increasing the density threshold the number of connections increased. With a density threshold of 50% the difference between eyes-open and eyes-closed condition start to be not noticeable probably because we are including a lot of low relevant values.

In ***Figure 3*** we consider a second frequency value 30 Hz belonging to a different EEG rhythm(beta). At frequency 30Hz we notice less difference between the two conditions(EO, EC) with respect to the differences at frequency 10 Hz.

The EEG analysis can also be performed focusing on just 19 channels in order to have more interpretable results by non-neurologists, e.g., nurses, residents or intensivists, by preventing “information overload”.

In this case we used the second technique(based on validation procedure) in order to obtain two networks for both eyes-opened and eyes-closed conditions. In ***Figure 4*** we show the two adjacency matrices obtained with this second method. In ***Figure 5*** we show a topographical representation of these two weighted networks highlighting the grade of the connections. We notice that in eyes-opened condition we have more connections but just channel Cz can be considered central. Instead in eyes-closed condition we have Cz, O1 and Pz which can be considered central.

Graph theory

Brain networks can be analyzed by measuring different aspects of their structure. Measures of integration such as **average path length** are important to understand the ability of the network to rapidly combine specialized information from distributed brain regions. Measures of segregation such as **average cluster coefficient** represent the ability for specialized processing to occur within densely interconnected groups of brain regions (clusters or modules). Eventually, measures of centrality such as **degree, in/out degree** can highlight important brain regions (hubs) often interact with many other regions, facilitate functional integration, and play a key role in network resilience to insult.

We analyzed our networks from a global perspective (average path length, average cluster coefficient) and from a local one (degree, in/out degree). In the case of the two networks obtained with DTF, density=20% and the relevant frequency at 10 Hz we obtained the result recapped in ***Table 2.*** In ***Table 3*** we put the global indices for the same networks but in this case they are obtained using PDC estimator. We notice that the main difference between the two estimators is the average path length which (with PDC is equal to 1.9 for EO and 2.1 for EC while with DTF is equal to 0.68 for EO and 0.84 for EC).

In ***Table 4*** we show how the global indices change by changing density of the network. We notice that average clustering coefficient increases by increasing the density in both conditions(EO, EC)**.** Regarding the average path length, it increases for both condition until 50% of density value when it decreases.

In ***Figure 6*** we show a topographical representation of the local indices by mapping the color of the edges with respect to its local index. Here we can appreciate a property of the two networks: the nodes in both cases have the same number of out-degree centrality so the degree centrality is entirely caused by in-degree. We noticed the central nodes for EO are F3, Fz, Cz and Pz while for EC are many more such as F3, Fz, Cz ,Pz, O1, P3, C3, O2 and P8. In ***Table 5*** we put the results of graph indices of the network in *Figure 3*(beta rhythm - 30Hz). In ***Table 6*** we put the results of graph indices of the weighted version of the network obtained with DFT, density=20% and frequency at 10Hz.

Another important characteristic of networks is the **small world** property. "Small-world networks, according to Watts and Strogatz, are a class of networks that are "highly clustered, like regular lattices, yet have small characteristic path lengths, like random graphs." These characteristics result in networks with unique properties of regional specialization with efficient information transfer." [3]

In our case we used the definition of small-worldness index ([3] "We propose a new small-world metric, ω (omega), which compares network clustering to an equivalent *lattice* network and path length to a *random* network, as Watts and Strogatz originally described").

We computed this index in both networks: eyes-opened and eyes-closed obtained with DTF, density=20% at frequency 10 Hz. The value for eyes-opened network is equal to **0.03202**, for eyes-closed is equal to **0.03936**. A small-world network should have a value of omega similar to 0. According to these results both two networks slightly seem to have small world properties.

Motif analysis

The motifs are a class of small and recurrent networks of 3 or 4 edges, which are fundamental building blocks of more complex networks[6].

A motif analysis was conducted on the two networks, in order to find recurrent and statistically significant patterns that characterize the resting state functional connectivity.

These sub-graphs, defined by a particular pattern of interactions between EEG channels, may reflect an underlying scheme with which brains efficiently achieve specific functions. Indeed, motifs are of high importance largely because they may reflect functional properties. Although network motifs may provide a deep insight into the network's functional abilities, their detection is computationally challenging. This is the main reason why our motif analysis doesn't go further than the research of 4-nodes configurations, and is actually mainly focused on the 3-nodes patterns.

We are still considering the networks obtained through cutting the DTF causality values at a threshold that yields networks with 20% densities, and again taking only values at the chosen alpha rhythm frequency of 10 Hz.
Our analysis is achieved through the mfinder algorithm, developed and published by Kashtan et al, of which a convenient software version (that we used) is implemented by the Uri Alon Lab [4].
Regarding the 3-nodes motifs, we found after applying the algorithm that in the Eyes-Open network there are 3 motifs (*pattern ids:* **46, 108, 238**[1]) and 5 anti-motifs (patterns that are significantly <u>under-represented</u> in the network, *with ids:* **6, 14, 36, 74, 78**[1]). The significance was evaluated with p-values < 0.025 for motifs, and p-values > 0.975 for anti-motifs.

[1] See ***Figure 7*** for graphical representations of patterns related to motifs and anti-motifs ids

Pattern Id	46	108	238	6	14	36	74	78
Real Freq.	87	1569	99	514	66	8485	1444	39
Rand Freq.	60.6 ± 5.4	1492.7 ± 18.4	81 ± 3.8	640.3 ± 28	94.5 ± 11.2	8561.3 ± 36.1	1572.4 ± 31.8	81.9 ± 8.4

The complete output of the mfinder tool for the Eyes-Open network is reported in `*motif_open_OUT_3dim.txt*`.

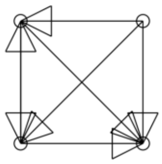
For the Eyes-Closed network, there are 2 motifs (*pattern ids:* **38, 46**[1]) and 6 anti-motifs (*pattern ids:* **6, 14, 36, 74, 78, 98**[1]), with the same levels of significance as above.

Pattern Id	38	46	6	14	36	74	78	98
Real Freq.	1958	108	660	109	7470	1515	81	14
Rand Freq.	1839.7 ± 37.8	88 ± 7.7	839 ± 33.8	151.1 ± 14.4	7608.2 ± 41.7	1640.2 ± 34.8	109.9 ± 9.2	33.1 ± 6.7

The complete output of the mfinder tool for the Eyes-Closed network is reported in `*motif_close_OUT_3dim.txt*`.

We noticed that the pattern **46** is a <u>motif</u> in both networks, and patterns **6, 14, 36, 74, 78** are <u>anti-motifs</u>, suggesting that these patterns may be characterizing for the functional connectivities of the brain in the resting state.
We focused our analysis on a specific pattern, i.e. that of the common and most frequent anti-motif with id **36**, corresponding to the subgraph structure **A** → **B** ← **C**. In a graphical comparison of the topographical representations of the two networks, reported in ***Figure 8***, we found that the two networks have many traits in common, especially looking at the centrality of three channels: **O1, P4, P8**. This suggests that connections in these brain areas are characterizing the resting state in both cases of open or closed eyes.
The same analysis was done with 4-nodes configurations, but since the possible subgraphs with 4 nodes are 199, results are much less interpretable.
We found a common motif in the two networks, with id **2524** and corresponding to the pattern showed below, with **pval<0.05** in both networks and with frequencies of **396** (against a random average of *271.6 ± 45.3*) in the Eyes-Open network and **1133** (against a random average of *757 ± 102.7*) in the Eyes-Closed network.

id2524



Many common anti-motifs were found, but for further analysis we report the results in `*motif_open_OUT_4dim.txt*` and `*motif_close_OUT_4dim.txt*`.

Finally, we focused our analysis on the Parieto-Occipital region, in particular on the channel PO8, in order to find all 3-nodes motifs in which it is involved. We did this by parsing a different output file of the software mfinder, which outputs all members for all the patterns found by the algorithm. These outputs for the two networks are stored in the files `*motif_open_MEMBERS_3dim.txt*` and `*motif_close_MEMBERS_3dim.txt*`.
We found that the PO8 channel appears between the members of the motif with id **108** for the Eyes-Open network, and in the motif with id **38** for the Eyes-Closed network.

Communities detection

One of the most relevant features of graphs representing real systems is community structure, or clustering, i.e. the organization of vertices in clusters, with many edges joining vertices inside the same cluster, and comparatively few edges joining vertices belonging to different clusters. Such clusters, or communities, can be considered as fairly independent compartments of a graph, playing a similar role like, e.g., the tissues or the organs in the human body [7]. In a brain, these clusters represent synchronized areas of the brain that show most connections with other members of the same community during a particular state (resting state in our case), and can help in reducing the complexity of the analysis of neural functional connectivity. In order to detect the communities two different algorithms were applied: the *modularity-based* ***Newman***'s algorithm and the *information theory-based* ***Infomap*** (based on map function).

Results of both community detection algorithms on both networks are shown in ***Figures 9,10*** through topographical representations of the communities on all the 64 channels.

They show that both **Infomap** and **Newman**'s algorithms detect, with small differences, the same main communities. Main differences are due to the fact that the infomap algorithm erases all single nodes, showing those belonging to actual communities, while the modularity-based method keeps them as singletons. Also, it is shown that there is a substantial difference between the Eyes-Opened and Eyes-Closed networks, that is the emergence of a large community in the left Parieto-Occipital region in the Eyes-Closed state, together with the two main communities detected also in the Eyes-Closed network, one in the right Parieto-Occipital region and the biggest in the Frontal-Central region. This suggests that, at the observed alpha frequency of 10Hz, the left Parieto-Occipital region is independent from other brain areas during resting state with closed eyes, but becomes more involved in connections with the Frontal area when eyes are opened, thus being inserted in the same big (red) community.

Conclusion

From a macroscopic perspective the average path length and binary adjacency matrix suggest that the eyes-closed network has more concentrated connections(more centralization around specific channels). The small-worldness index(omega) has no variation with respect to both conditions.
From a microscopic perspective we notice that different nodes are central to the two networks (by degree comparisons), but **F3**, **Fz**, **Cz** and **Pz** are central to both, and may be characterizing the resting state. In E-C we have the double of the nodes which can be considered as central by degree, again characterizing higher centralization in this condition.
From a mesoscopic perspective, significant motifs with 3 and 4 node patterns were found appearing in both networks (respectively id **46** and id **2524**), and these can be considered as features of the resting state functional connectivity in the brain of the analyzed subject.
The main feature appearing only in Eyes-closed condition is the detection of a large community in the left Parieto-Occipital area, that is incorporated with the larger Frontal-Central area in the Eyes opened condition, implying an increased number of connections between nodes belonging to these two broad areas. But, a common and stable community is found in the right Parieto-Occipital region in both conditions, suggesting that the isolation of channels belonging to this area from other channels (outside the community) is a specific trait in the resting state of the brain of the analyzed subject. Important results may be obtained by comparing these outcomes with those related to other subjects, especially in the case of manifest pathological conditions.

References

1. Connectome: Graph theory application in functional brain network architecture
2. Chapter 1 - An Introduction to Brain Networks
3. Telesford, Joyce, Hayasaka, Burdette, and Laurienti (2011). The Ubiquity of Small-World Networks | Brain Connectivity
4. motif analysis tool: Network Motif Software | Uri Alon
5. https://www.sciencedirect.com/science/article/pii/S2467981X17300276
6. Analysis of Structure and Dynamics in Three-Neuron Motifs
7. Community detection in graphs
8. A short study of abbreviated EEG

Tables and Figures

Task 1	**Class**	**Task 2**	**Class**	**Task 3**	**Class**	**Task 4**	**Class**
1.1	*mandatory*	**2.1**	*mandatory*	**3.1**	*mandatory*	**4.1**	*mandatory*
1.2	*A*	**2.2**	*D*	**3.2**	*C*	**4.2**	*B*
1.3	*A*	**2.3**	*B*	**3.3**	*C*	**4.3**	*C*
1.4	*D*	**2.4**	*C*	**3.4**	*E*		
1.5	*C*	**2.5**	*B*				
1.6	*B*	**2.6**	*B*				
		2.7	*C*				

***Table 1**: list of task chosen for the project (**we chose all of them**)*

Index	**EYES-OPENED**	**EYES-CLOSED**
average clustering coefficient	0.52641	0.45210
average path length	0.68576	0.84275
top 10 node by degree	'F3..', 'Cpz.', 'F5..', 'Cp4.', 'F1..', 'Fz..', 'Cp3.', 'Cp1.', 'Po3.', 'Fc2.'	'Cpz.', 'Poz.', 'F5..', 'O1..', 'Pz..', 'F3..', 'Cz..', 'Fz..', 'Iz..', 'P1..'
top 10 node by in degree	'F3..', 'Cpz.', 'F5..', 'Cp4.', 'Fz..', 'F1..', 'Cp3.', 'Po3.', 'Fc2.', 'Cp1.'	'Poz.', 'O1..', 'F5..', 'Cpz.', 'F3..', 'Fz..', 'Pz..', 'Cz..', 'Iz..', 'Po3.'
top 10 node by out degree	'Af8.', 'Fp2.', 'Cp2.', 'Af4.', 'Poz.', 'Fc6.', 'C2..', 'C6..', 'Af7.', 'F8..'	'Ft8.', 'Cpz.', 'Af8.', 'Ft7.', 'T8..', 'Fc6.', 'C2..', 'Cp1.', 'P6..', 'Fc4.'

***Table 2**: recapped results of global and local indices for networks(OE, CE) estimated with DTF, density=20% and frequency at 10 Hz*

Index	**EYES-OPENED**	**EYES-CLOSED**
average clustering coefficient	0.31573	0.31848
average path length	1.9067	2.14236

***Table 3**: recapped results of global indices for networks(OE, CE) estimated with PDC, density=20% and frequency at 10 Hz*

Network	***Average Clustering Coefficient***	***Average Path Length***
OE 10% density	0.22204	1.1555
CE 10% density	0.2497	1.6944
OE 30% density	0.40385	1.77207
CE 30% density	0.39247	2.0076
OE 50% density	0.56352	1.6031
CE 50% density	0.55838	1.5602

Table 4*: recapped results of global indices for networks(OE, CE) estimated with PDC for different values of network density and frequency at 10 Hz.*

Index	**EYES-OPENED**	**EYES-CLOSED**
average clustering coefficient	0.42225	0.47951
average path length	0.9528	1.20362
top 10 node by degree	'Cpz.', 'Cp1.', 'Fz..', 'Fc1.', 'P1..', 'F3..', 'Cz..', 'C3..', 'F5..', 'Pz..'	'F3..', 'Cp1.', 'C3..', 'F5..', 'Fz..', 'P6..', 'C1..', 'Cp3.', 'Fc1.', 'Cz..'
top 10 node by in degree	'Cpz.', 'Fc1.', 'Fz..', 'Cp1.', 'Cz..', 'P1..', 'F5..', 'C3..', 'F3..', 'Pz..'	'F3..', 'Cp1.', 'F5..', 'C3..', 'Fz..', 'C1..', 'P6..', 'Cp3.', 'Cz..', 'Cpz.'
top 10 node by out degree	'C5..', 'F3..', 'Fc5.', 'Af8.', 'Fc3.', 'Fp1.', 'Fp2.', 'F8..', 'C3..', 'Af7.'	'Fc4.', 'F3..', 'Fc6.', 'C4..', 'C6..', 'Cp6.', 'P2..', 'Fc3.', 'Fc2.', 'Af8.'

Table 5*: recapped results of global and local indices for networks(OE, CE) estimated with DTF, density=20% and frequency at 30 Hz(beta rhythm)*

Index	**EYES-OPENED**	**EYES-CLOSED**
top 10 node by degree	'F3..', 'F5..', 'Fz..', 'Cpz.', 'Cp4.', 'F1..', 'Fc2.', 'Cp3.', 'Po3.', 'Po4.'	'O1..', 'Cpz.', 'F3..', 'Fz..', 'F5..', 'Pz..', 'Poz.', 'Cz..', 'Po3.', 'Po4.'
top 10 node by in degree	'F3..', 'F5..', 'Fz..', 'Cpz.', 'Cp4.', 'Fc2.', 'F1..', 'Po3.', 'Po4.', 'Cp3.'	'O1..', 'Cpz.', 'F3..', 'Fz..', 'F5..', 'Pz..', 'Poz.', 'Po3.', 'Cz..', 'Iz..'
top 10 node by out degree	'Af8.', 'F8..', 'Fp2.', 'Af4.', 'Fc6.', 'Ft8.', 'F6..', 'Af7.', 'Fp1.', 'Fpz.'	'Ft7.', 'Fc6.', 'C5..', 'Fc4.', 'Ft8.', 'C3..', 'Af8.', 'C4..', 'C6..', 'C2..'

Table 6*: recapped results of local indices for the weighted networks(OE, CE) estimated with DTF, density=20% and frequency at 10 Hz*

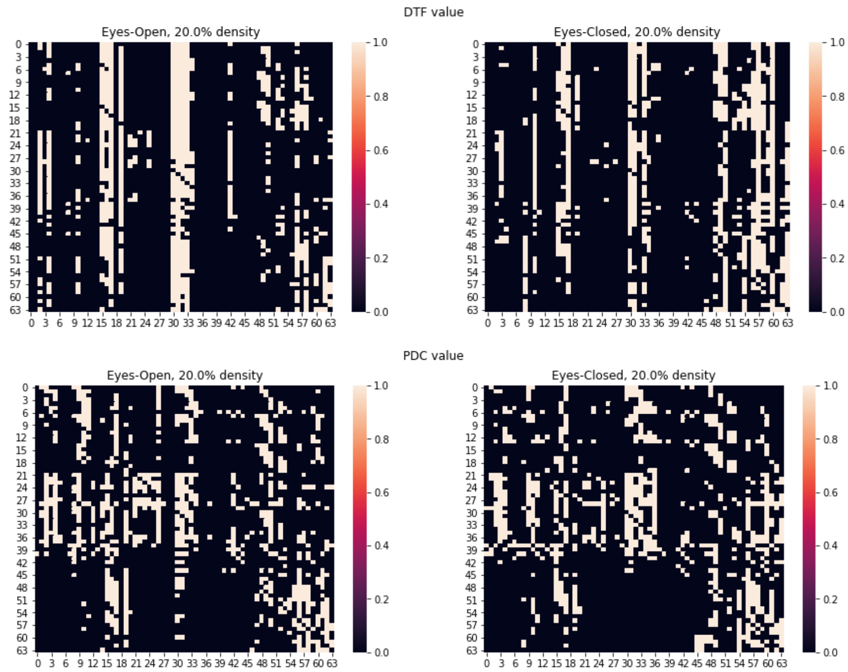


Figure 1. *Comparison of the adjacency matrices built with the two causality measures at **frequency 10 Hz**, cut at a threshold such that the resulting networks have density 20%, for both Open-Eyes and Closed-Eyes EEG*

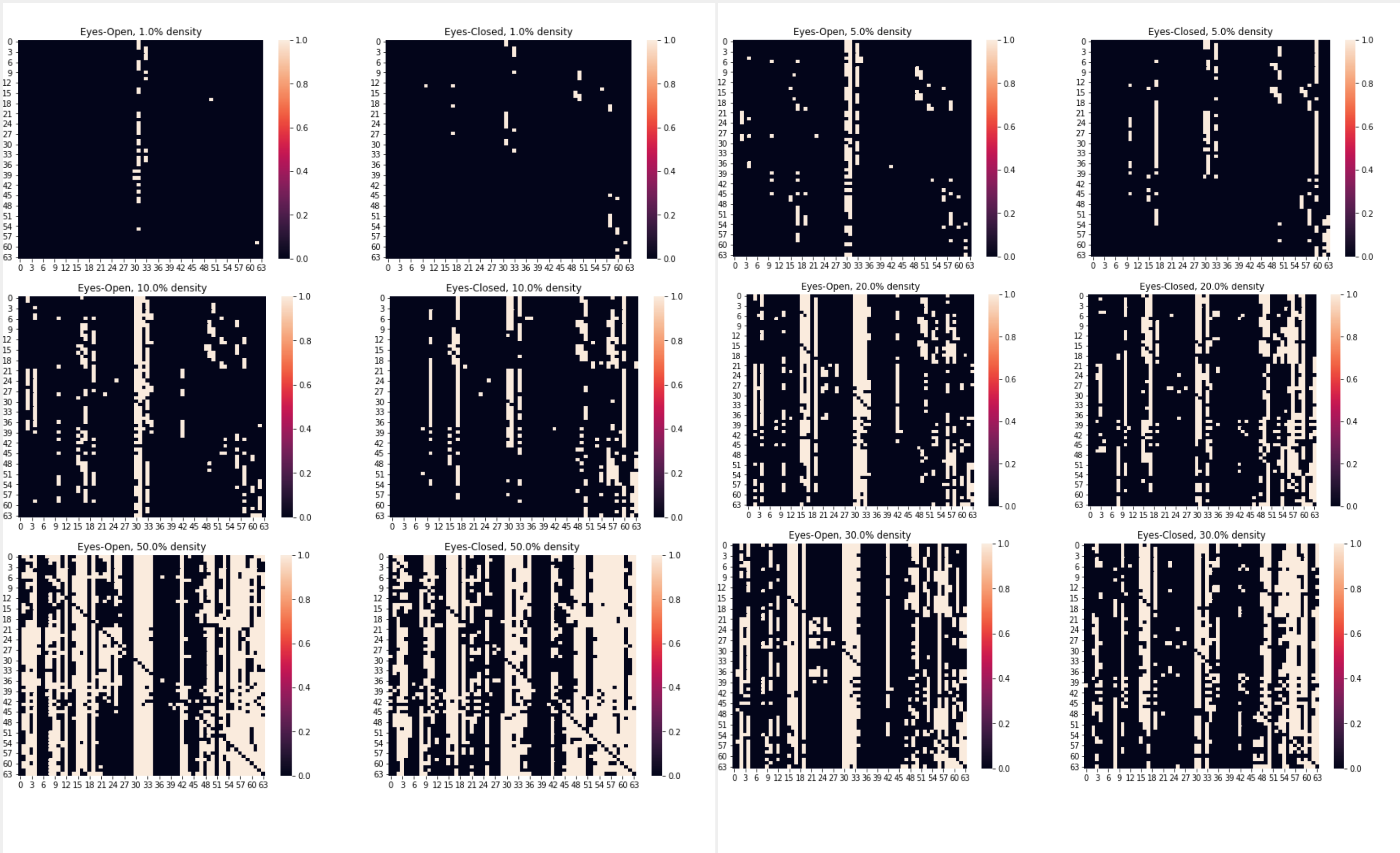


Figure 2. *Behaviour of the adjacency matrices built with DTF at* ***frequency 10 Hz*** *changing density(1%,5%,10%,30%,50%)*

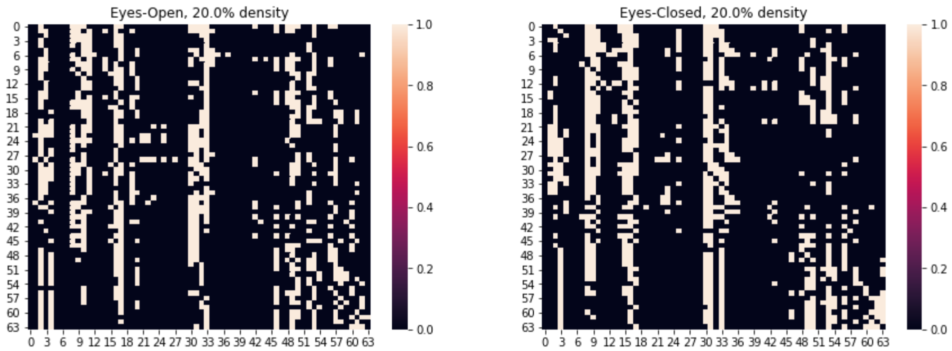


Figure 3. *Adjacency matrices built with DTF at* ***frequency 30 Hz*** *density=20%*

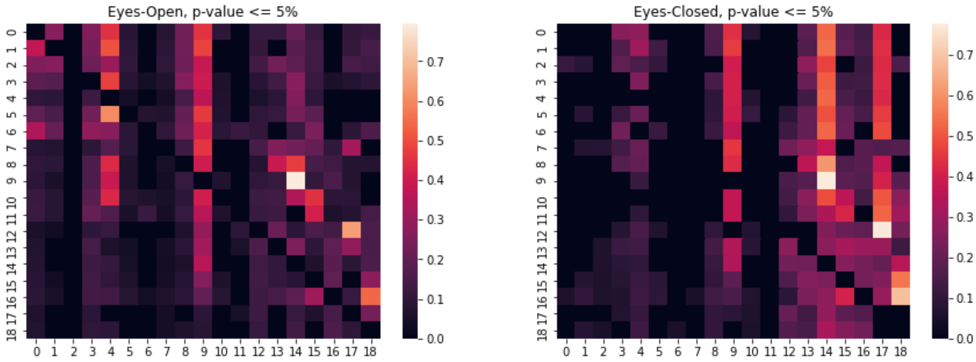


Figure 4. *Weighted adjacency matrices built with DTF at* ***frequency 10 Hz*** *using a validation resampling procedure(p-value <=5%)*

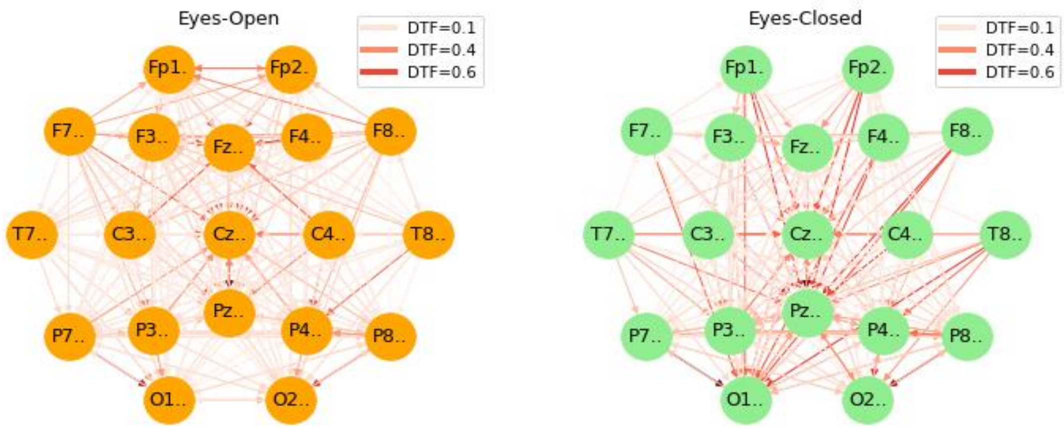
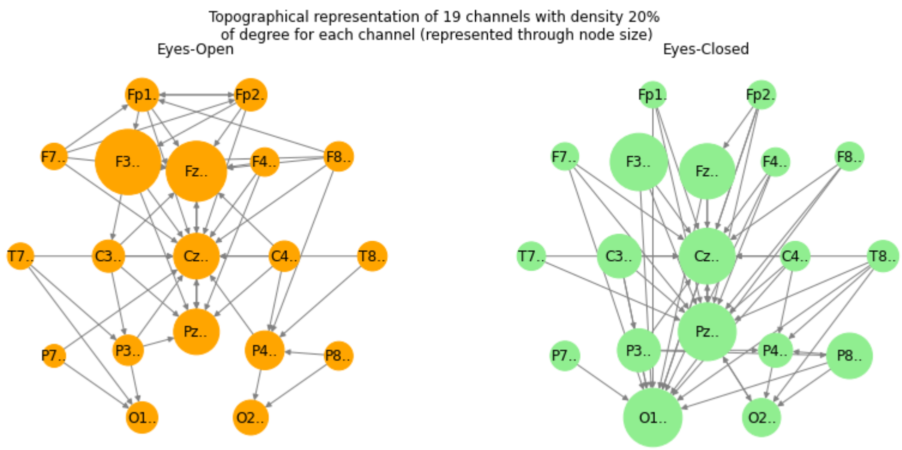


Figure 5. *Topographical representation of the weighted networks built with DTF at* ***frequency 10 Hz*** *using a validation resampling procedure(p-value <=5%)*



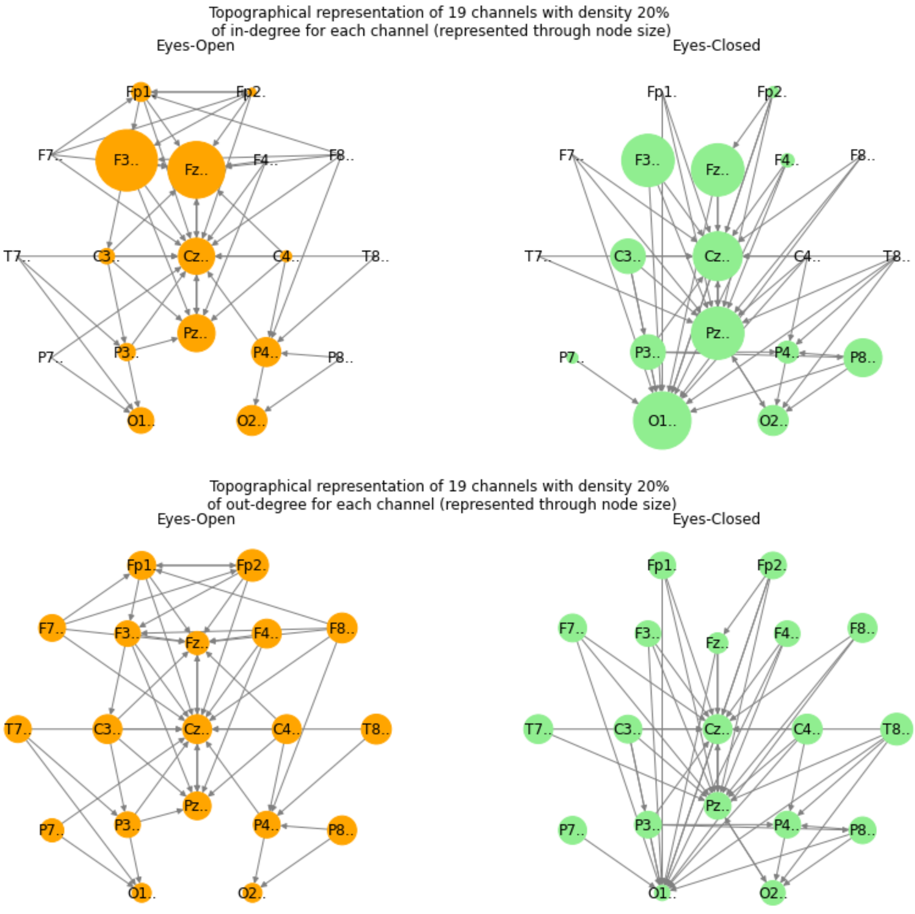


Figure 6. *Topographical representation of 19 channels with density 20% of local indices*

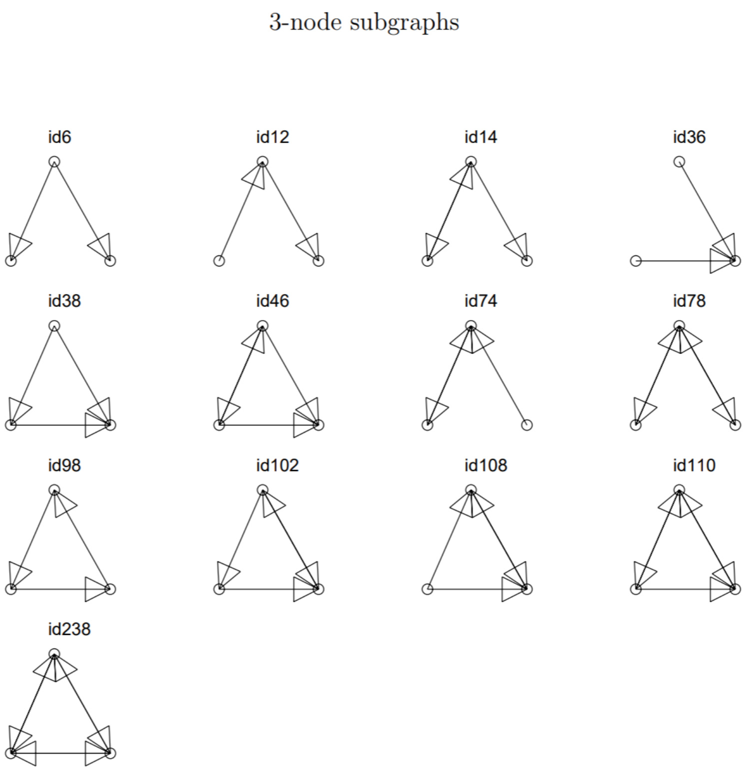


Figure 7. *3-node patterns graphical representation, extracted from the [Motif Dictionary]*

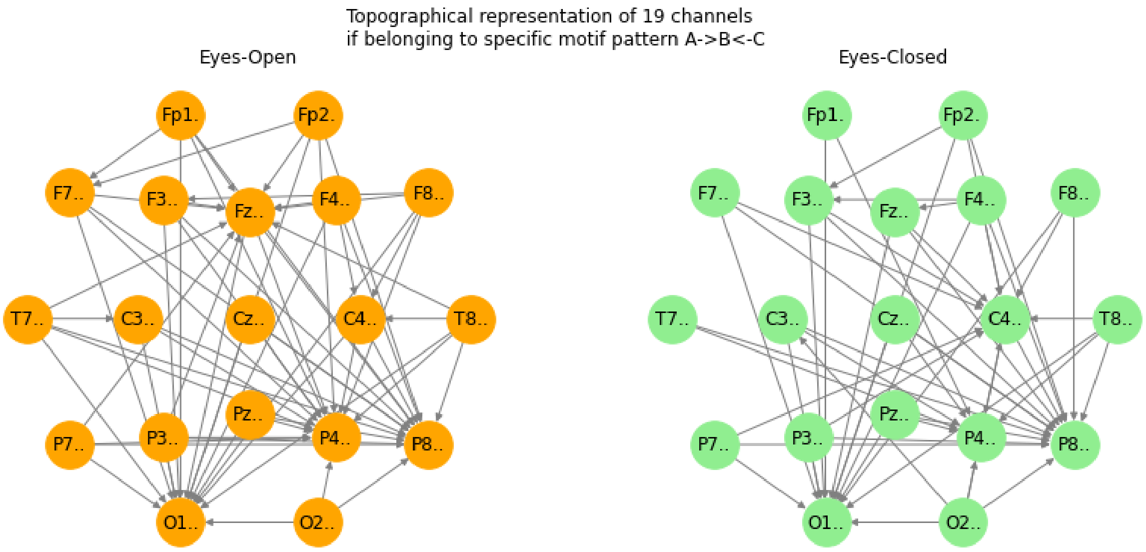


Figure 8. *Topographical representation of the resulting networks selecting only the edges belonging to patterns of the type **A** → **B** ← **C** (id **36**)*

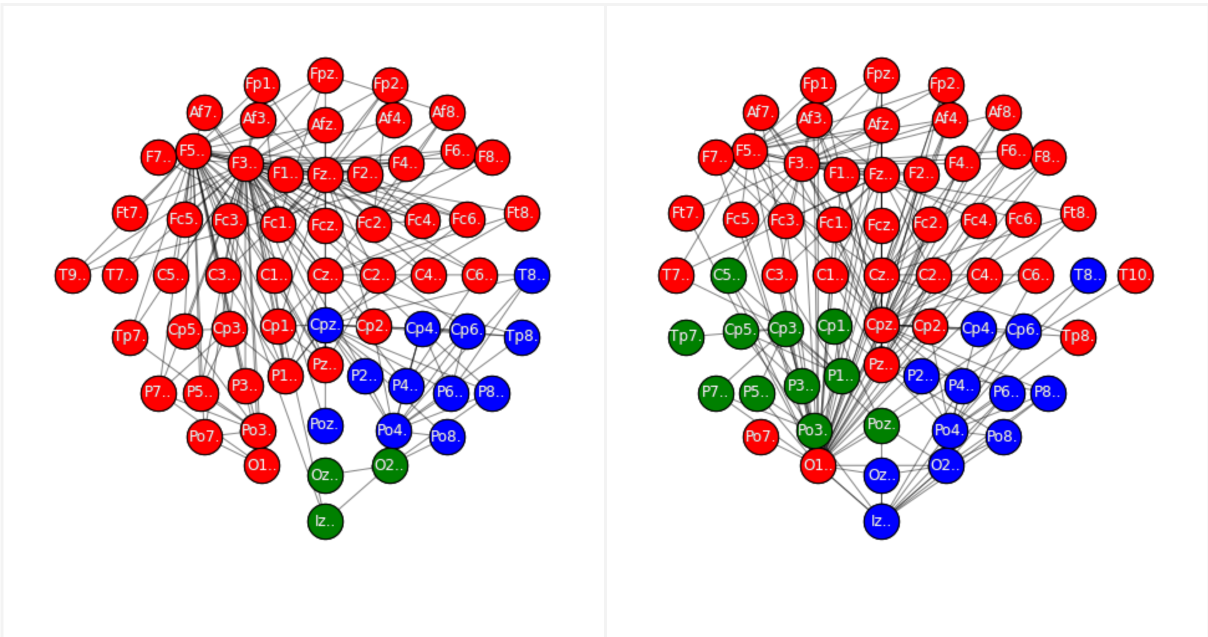


Figure 9. *Topographical representation of the community structure detected with **infomap**-algo**(left eyes-opened, right eyes-closed)**. The single nodes are cut off.*

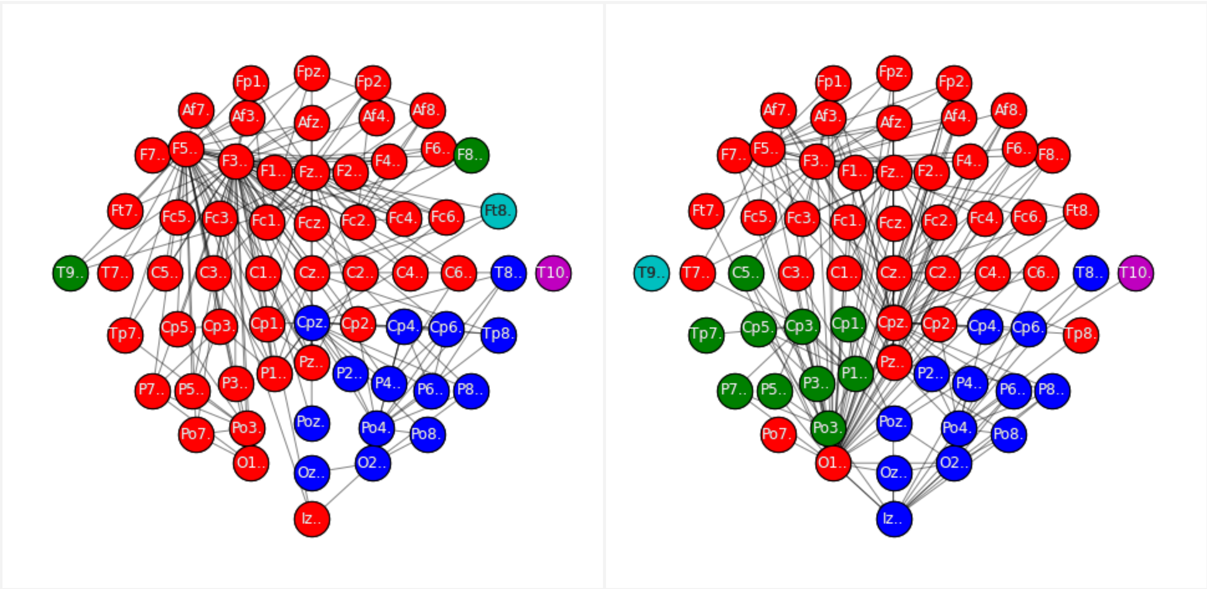


Figure 10. *Topographical representation of the community structure detected with **newman**-algo **(left eyes-opened, right eyes-closed)**.*