2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

2021 43rd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC) | 978-1-7281-1179-7/21/$31.00 ©2021 IEEE | DOI: 10.1109/EMBC46164.2021.9630173

Multi-layer analysis of multi-frequency brain networks as a new tool to study EEG topological organization*

Maria Grazia Puxeddu, Manuela Petti, and Laura Astolfi, *Member, IEEE*

***Abstract*— Oscillatory activity rising from the interaction among neurons is widely observed in the brain at different scales and is thought to encode distinctive properties of the neural processing. Classical investigations of neuroelectrical activity and connectivity usually focus on specific frequency bands, considered as separate aspects of brain functioning. However, this might not paint the whole picture, preventing to see the brain activity as a whole, as the result of an integrated process. This study aims to provide a new framework for the analysis of the functional interaction between brain regions across frequencies and different subjects. We ground our work on the latest advances in graph theory, exploiting multi-layer community detection. In our multi-layer network model, layers keep track of single frequencies, including all the information in a unique graph. Community detection is then applied by means of a multilayer formulation of modularity. As a proof-of-concept of our approach, we provide here an application to multi-frequency functional brain networks derived from resting state EEG collected in a group of healthy subjects. Our results indicate that α-band selectively characterizes an inter-individual common organization of EEG brain networks during open eyes resting state. Future applications of this new approach may include the extraction of subject-specific features able to capture selected properties of the brain processes, related to physiological or pathological conditions.**

I. INTRODUCTION

Brain activity and functioning can be investigated via network science, by means of functional networks in which different brain areas are linked according to measures of correlation, causality, or other statistical dependencies [1], [2]. In the recent years, with neuroimaging datasets becoming richer and brain connectivity estimation methods more and more informative, the classical tools of network analysis were extended to a multi-layer space, where several information can be encoded in different layers of a multi-dimensional network [3]. This framework allows exhaustive investigations where multiple features of brain activity are studied with their reciprocal coupling, without aggregating or discarding useful data. The different layers can include the properties of the brain networks across time, subjects, tasks, or clinical conditions and study their coupling.

Particularly interesting, and mostly unexplored, is the case in which the network layers encode functional brain networks estimated at different frequencies. In fact, standard analyses usually study the different frequencies separately or focus on single frequency bands. On the other hand, a multi-frequency analysis could lead to a better understanding of the actual brain functioning, which produces oscillations at different frequencies simultaneously. In a contextual work [4] brain connectivity networks at four frequency bands (α, β, low-γ and high-γ) were extracted from MEG data and encoded in a multi-layer network, returning statistically significant differences in the occipital α-band network between subjects with schizophrenia and a control group. Functional MRI data were also used to build a frequency-based multi-layer network to compare schizophrenic subjects with matched healthy subjects [5]. Results suggested that the hubs of this network are distributed differently between the two groups. Both studies support the hypothesis that physiological mechanisms underlying brain activity are expressed across - as well as within - different frequency domains and suggest that cross-frequency indices can be used as biomarkers of pathological conditions.

In this work, we aim to show how to use multi-layer models to study multi-frequency brain networks derived from electroencephalographic (EEG) signals. Compared to fMRI and MEG, EEG boasts advantages such as high temporal resolution and portability, which allow to analyze a broad spectrum of frequencies over a wide range of subjects, clinical conditions, and tasks. We aim to investigate the topological properties of EEG-based multi-frequency brain networks, focusing on their modular structure, a hallmark of brain networks, consisting of the presence of communities of densely interconnected nodes [6]. Specifically, here we propose an approach to explore the relation between connectivity at different frequencies and inter-individual variability of the brain organization. In fact, uncovering common - as well as subject-specific - patterns can be crucial for many applications, spanning from the definition of biomarkers to the design of biometric systems and brain computer interfaces, which are raising the interest of several studies in the literature (e.g. [7]).

To test our approach, we estimated resting state EEG networks in a group of healthy subjects by means of a spectral multivariate estimator called Partial Directed Coherence. Then, we built the multi-layer network and performed the subsequent multi-frequency module detection. Finally, the modular organization across frequencies was examined through indices that determine common patterns among subjects, to provide a characterization of the topological structure of the healthy brain at rest and to prove the usefulness of the proposed approach for multi-frequency modular analysis of EEG networks.

*Research supported by Sapienza "Progetti di Ateneo" RM11715C82606455, RP11816436CDA44C, and RM11916B88C3E2DE; by a BitBrain award (B2B Project) and by "Dipartimenti di eccellenza" fund (MIUR).

Puxeddu M.G.(corresponding author, email: puxeddu@diag.uniroma1.it), Petti M., and Astolfi L. are with the Department of Computer, Control and Management Engineering, University of Rome La Sapienza, Via Ariosto 25, 00185 Rome, Italy, and with IRCCS Fondazione Santa Lucia, Via Ardeatina 306, 00179 Rome, Italy.

II. METHODS

A. EEG recordings and preprocessing

EEG data were acquired in 45 healthy adults (24 male, age 26.7±5.2). All the participants gave informed consent prior to participation and recordings were approved by the local ethics committee. Data were collected at the Neuroelectrical Imaging and BCI Laboratory at IRCCS Fondazione Santa Lucia of Rome and were also used in [8], [9]. EEG was acquired with 61 electrodes (placed using the extended 10-20 International System) and sampling frequency 200Hz at rest with closed eyes (CE) and open eyes (OE) for 60 seconds. Data processing included band pass filtering in the range 1-40Hz and artifact rejection by means of Independent Component Analysis.

B. Multi-frequency topological analysis

1) Multi-frequency network construction.

Functional connectivity was estimated through Partial Directed Coherence, or PDC [10] in the range 1-40Hz (optimal order: 19.3±2.95). Significance of functional links was tested via asymptotic statistics [11]. For each subject and condition (CE, OE) we build a multi-layer functional brain network by concatenating the adjacency matrices reporting PDC values among the electrodes at each of the 40 frequency bins. Thus, we obtained 90 (45 subjects × 2 conditions) multi-layer networks of dimensions 61×61×40 (number of electrodes × number of electrodes × number of frequency bins).

2) Multi-frequency community detection.

We investigated the topological organization of these networks through a multi-layer community detection analysis. Among the algorithms available for the task, we selected genLouvain, which is based on modularity optimization [12] and was already proven to be suitable for EEG brain networks [13]–[15]. Through a stochastic process, it estimates a partition of the network into modules by maximizing the modularity, a quality function that quantifies how strongly modules are internally connected in comparison with a chance level. We iterated the algorithm 100 times for each multi-layer network, to statistically evaluate the outcoming topological properties. Moreover, as multi-layer modularity optimization depends on a resolution parameter ω, which affects the coupling of partitions across layers (higher ω-values foster stronger coupling), we run the algorithm with three increasing ω-values (ω=[0.1, 0.3, 0.5]) chosen in accordance with previous studies [15]. To select the most informative among the three resulting sets of differently resolved multi-layer partitions, we used a criterion based on the physiological division between frequency bands. We selected the set in which partitions were, at the same time, maximally similar within, and dissimilar among, the individual EEG bands, defined for each subject according to the Individual Alpha Frequency (IAF) [16]: δ [1, IAF-7]; θ [IAF-6, IAF-3]; α [IAF-2, IAF+2]; β [IAF+3, IAF+14]; γ [IAF+15, 40Hz]. To this purpose, we exploited the Variation of Information (VI) [17], an index of dissimilarity between two partitions. VI spans the range [0,1], where the lower value indicates identical partitions. For each subject we computed the VI between the partitions at different frequency, obtaining VI matrices of dimension 40×40, where the entry *ij* denotes the VI obtained comparing the partition at frequency *i* with the one at frequency *j*. Then, we selected the ω returning multi-frequency partitions where VI values were lowest within the four bands and highest between them.

3) Inter-subject variability of the modules

Downstream the identification of the most physiologically informative multi-frequency modular structure, we explored the inter-subject variability of the modules across frequencies. Again, we used the VI computed between each pair of subjects for the same frequency layer as a measure of variability. This quantified how the communities are consistent across subjects at different frequencies. Finally, we provide a scalp map of the communities at the frequency where the consistency is highest. To this aim, we exploit consensus clustering [18], to obtain for each subject a single partition out of the100 iterations.

III. RESULTS

1) Multi-frequency community detection.

The multi-frequency community detection relative to the three ω-values returned three sets of partitions, enclosed in matrices of dimension 61×40 (number of nodes × number of frequencies), where entries are integers indicating the module to which each node belongs. In Figure 1 we report the obtained VI matrices, which assess the similarity of the partitions across layers. As expected, higher ω values lead to a stronger coupling of the partitions across frequencies (for ω=0.5, all entries are close to 0). Lower ω, instead, results in partitions coherent with the conventional division in bands. Here, the entries of the matrix are close to 0 within the bands and

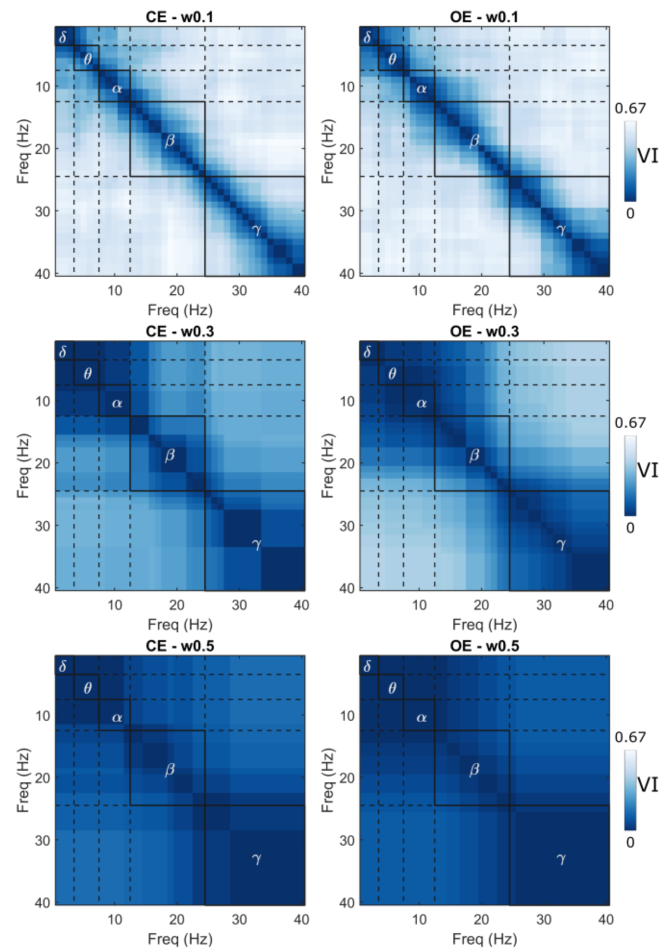

Figure 1. Variation of Information (VI) matrices of a representative subject for the two conditions OE/CE (columns) and the three ω-values (rows). VI values are reported through a color code in the scale of the blues (lowest VI values go in the direction of darkest blue). The black grid indicates the classical EEG frequency bands (δ, θ, α, β, γ).

increase outside. Thus, for the following analysis, we selected the set of partitions obtained with ω=0.1. This result applies to all subjects and both OE and CE networks, and it is consistent with the guidelines provided in [15].

2) Inter-subject variability of the modules.

Inter-subject variability was analyzed by computing the VI pairwise between all subjects for each frequency and then averaging these values. Results are reported in Figure 2, where the averaged values are reported along frequencies and for each iteration of the optimization algorithm. During CE, the frequency does not significantly affect the variability of the community structure among subjects (values of VI are consistent throughout the frequency spectrum). In contrast, during OE, we observe that VI values are reduced in a specific range of frequencies (around 10Hz, i.e. in the α-band) with respect to the rest of the spectrum, meaning that in this range partitions tend to be more consistent across subject. Specifically, the similarity is maximal around 10 Hz and decreases with the distance from this frequency value.

In Figure 3 we reported the modules most consistent among subjects, underpinning the functional networks at 10Hz. To obtain these common modules we first selected the partitions of the 10th layers (100 partitions for each subject, one for every iteration of the optimization algorithm). Then, as described in the Methods section, we computed consensus

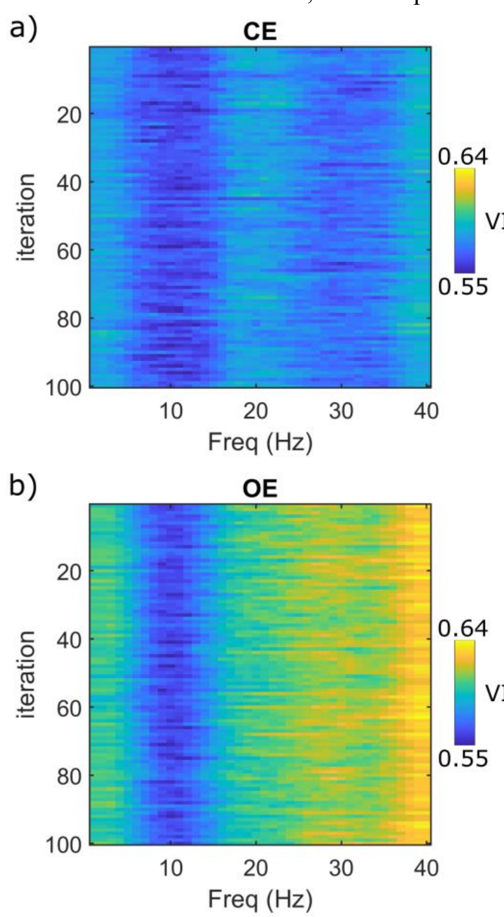

Figure 2. Inter-subject variability along frequencies. For the two conditions CE (panel a) and OE (panel b) the images represent the average values of VI computed pairwise between all subjects at each frequency bin and each iteration of the algorithm. VI values are reported through a color code ranging from blue (low VI, similar partitions) to yellow (high VI, distant partitions).

clustering [18] to obtain a single consensus partition for each subject. Finally, we plot on a scalp map only those appearing in at least 45% of the group. As a result, in the CE condition we obtained 5 consistent clusters among subjects, including (i) the frontal, (ii) the parieto-occipital, (iii) the central-left, (iv) the central, and (v) the central-right electrodes. During OE the spatial distribution of the clusters is similar to CE, except for the parieto-occipital module, which results split in two sub-modules, spanning the posterior-left and posterior-right hemispheres, respectively. Moreover, during OE, these parietal modules involve also more central and anterior electrodes, even if with lower percentages across subjects.

IV. Discussion and Conclusion

This work aims to provide a framework where functional connectivity of EEG-derived brain networks is analyzed taking into account simultaneously the information at different frequencies. So far, EEG network analysis consists of focusing on single bands separately or aggregating the information irrespectively of the frequency content. However, each frequency interval contains unique physiological information about the brain activity, and at the same time brain oscillations are a product of the global brain functioning. The theory of multi-layer networks provides the mathematical instruments to address this issue. Multi-layer network analysis was previously used to see how the topological properties of the brain functional networks change in time [19], or among subjects [20]. Here we propose a multi-layer framework in which layers encode the EEG functional connectivity at different frequencies, and we focus on the modular organization of the resulting networks.

The topological analysis we pursued led to partitions of the multi-frequency brain networks at rest into physiologically informative modules, that have a good overlap with previously observed resting state networks [21]. These modules show a good consistency within standard EEG bands, while diverging at frequencies belonging to different bands. We focused on the inter-subject variability of these partitions along frequencies, finding that OE networks distinctively show a common pattern in an interval centered on 10Hz. This result suggests that the frequencies characterizing the condition (the α-band, which has a distinctive role in OE and CE resting state) drive a consistent topological organization of the healthy brain network. Future works will elucidate if similar results can be found during specific tasks or in pathological conditions, where the proposed method could support deriving prognostic indices or biomarkers of the specific pathology.

The results here reported show how a multi-layer community analysis can characterize similar conditions like resting states with OE and CE. We found that the α-band selectivity of the inter-individual differences is specific of OE condition, and showed that the modules characterizing CE and OE subtend partially different circuits. The stronger difference lies in the occipital area, where the single module observable during CE is divided in two hemispheric-specific modules at OE. Moreover, while in CE this module is confined in the posterior part of the scalp, during OE the two resulting modules incorporate also more anterior, spatially non-adjacent nodes. We can hypothesize that these antero-posterior circuits may subtend attentional processes, active at OE, when visual stimuli are processed.

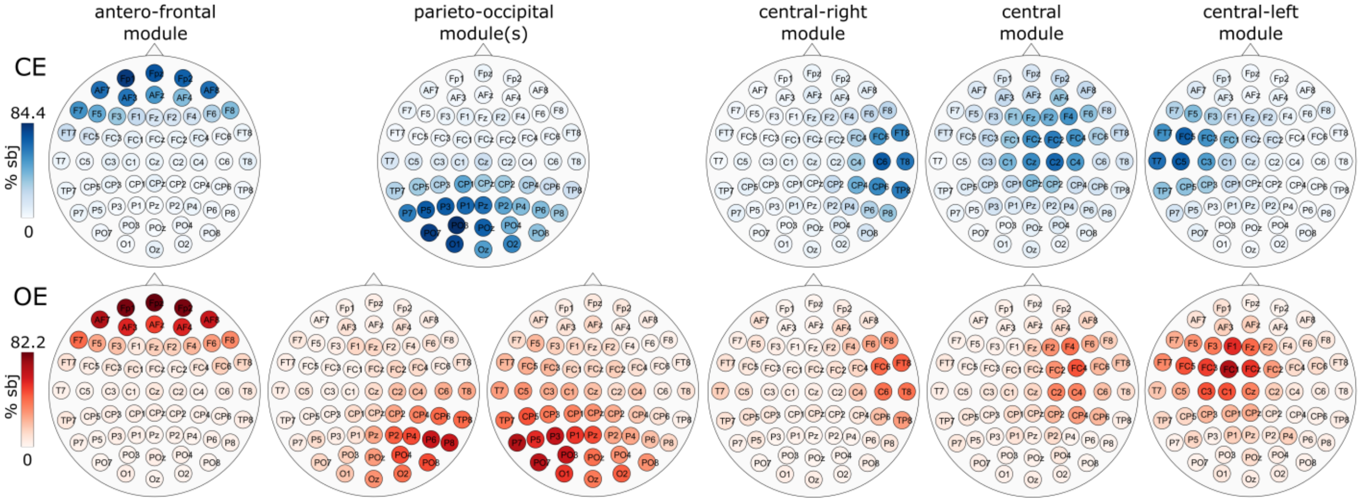

Figure 3. Modules resulting from consensus clustering between the 45 subjects at 10Hz, in CE (first row) and OE (second row). The electrodes are colored in blue (CE) or red (OE) with an intensity proportional to the number of subjects in which that node belongs to that cluster.

In conclusion, with this study we aimed to show that EEG networks can be successfully used for multi-frequency multi-layer network analysis. Previous works based on fMRI [5] and MEG [4] pointed out the need of integrating cross-frequency connectivity information. The use of EEG may open the way to future, more clinically oriented studies, exploiting the high temporal resolution of the EEG signals to extend analysis to a broad frequency spectrum with respect to fMRI, while taking advantage of the portability of the EEG instrumentation, which is of paramount importance in application at the patients' bedside or in other challenging clinical conditions.

Acknowledgment

We thank Dr. Donatella Mattia and the Neuroelectrical Imaging and BCI Laboratory of IRCCS Fondazione Santa Lucia of Rome for providing us the EEG raw data.

References

[1] D. S. Bassett e O. Sporns, «Network neuroscience», *Nature Neuroscience*, vol. 20, n. 3, pagg. 353–364, 03 2017.

[2] P. Tieri, L. Farina, M. Petti, L. Astolfi, P. Paci, e F. Castiglione, «Network Inference and Reconstruction in Bioinformatics», in *Encyclopedia of Bioinformatics and Computational Biology*, S. Ranganathan, M. Gribskov, K. Nakai, e C. Schönbach, A c. di Oxford: Academic Press, 2019, pagg. 805–813.

[3] M. De Domenico, «Multilayer modeling and analysis of human brain networks», *GigaScience*, vol. 6, n. 5, 05-01 2017.

[4] M. J. Brookes *et al.*, «A multi-layer network approach to MEG connectivity analysis», *NeuroImage*, vol. 132, pagg. 425-438, mag. 2016.

[5] M. De Domenico, S. Sasai, e A. Arenas, «Mapping Multiplex Hubs in Human Functional Brain Networks», *Front. Neurosci.*, vol. 10, 2016.

[6] O. Sporns e R. F. Betzel, «Modular Brain Networks», *Annual Review of Psychology*, vol. 67, pagg. 613–640, 2016.

[7] S. M. Pani *et al.*, «Subject, session and task effects on power, connectivity and network centrality: A source-based EEG study», *Biomedical Signal Processing and Control*, vol. 59, pag. 101891, mag. 2020.

[8] M. Petti, J. Toppi, F. Babiloni, F. Cincotti, D. Mattia, e L. Astolfi, «EEG Resting-State Brain Topological Reorganization as a Function of Age», *Comput Intell Neurosci*, vol. 2016, pag. 6243694, 2016.

[9] J. Toppi *et al.*, «Describing relevant indices from the resting state electrophysiological networks», in *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, ago. 2012, pagg. 2547–2550.

[10] L. A. Baccalá e K. Sameshima, «Partial directed coherence: a new concept in neural structure determination», *Biological Cybernetics*, vol. 84, n. 6, pagg. 463–474, 05-01 2001.

[11] J. Toppi, D. Mattia, M. Risetti, R. Formisano, F. Babiloni, e L. Astolfi, «Testing the Significance of Connectivity Networks: Comparison of Different Assessing Procedures», *IEEE Transactions on Biomedical Engineering*, vol. 63, n. 12, pagg. 2461–2473, 12 2016.

[12] P. J. Mucha, T. Richardson, K. Macon, M. A. Porter, e J.-P. Onnela, «Community Structure in Time-Dependent, Multiscale, and Multiplex Networks», *Science*, vol. 328, n. 5980, pagg. 876–878, 05-14 2010.

[13] M. G. Puxeddu, M. Petti, D. Mattia, e L. Astolfi, «The Optimal Setting for Multilayer Modularity Optimization in Multilayer Brain Networks*», in *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, lug. 2019, pagg. 624–627.

[14] M. G. Puxeddu, M. Petti, F. Pichiorri, F. Cincotti, D. Mattia, e L. Astolfi, «Community detection: Comparison among clustering algorithms and application to EEG-based brain networks», in *2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 07 2017, pagg. 3965–3968.

[15] M. G. Puxeddu, M. Petti, e L. Astolfi, «A comprehensive analysis of multilayer community detection algorithms for the application to EEG-based brain networks», *Front. Syst. Neurosci.*, vol. 15, 2021.

[16] W. Klimesch, «EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis», *Brain Research Reviews*, vol. 29, n. 2, pagg. 169–195, 04-01 1999.

[17] M. Meilă, «Comparing clusterings—an information based distance», *Journal of Multivariate Analysis*, vol. 98, n. 5, pagg. 873–895, 05-01 2007.

[18] A. Lancichinetti e S. Fortunato, «Consensus clustering in complex networks», *Scientific Reports*, vol. 2, pag. 336, 03-27 2012.

[19] M. G. Puxeddu, J. Faskowitz, R. F. Betzel, M. Petti, L. Astolfi, e O. Sporns, «The modular organization of brain cortical connectivity across the human lifespan», *NeuroImage*, vol. 218, pag. 116974, set. 2020.

[20] R. F. Betzel, M. A. Bertolero, E. M. Gordon, C. Gratton, N. U. F. Dosenbach, e D. S. Bassett, «The community structure of functional brain networks exhibits scale-specific patterns of inter- and intra-subject variability», *NeuroImage*, 07-07 2019.

[21] D. Mantini, M. G. Perrucci, C. D. Gratta, G. L. Romani, e M. Corbetta, «Electrophysiological signatures of resting state networks in the human brain», *PNAS*, vol. 104, n. 32, pagg. 13170–13175, ago. 2007.