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Frequency-Dependent Functional Connectivity of Brain Networks at Resting-State

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***Abstract*—Functional imaging methods such as resting-state fMRI allow to describe interactions among different areas of the brain, thus deriving a functional connectivity matrix of the entire brain network. Tracking functional relationships among different regions of interest can be applied, besides a pure modelling perspective, also to discovering procedures to detect brain diseases and anomalies, or pursuing rehabilitation of subjects with structural damages. However, network characterization is often regarded as frequency-independent, so that the frequency at which interactions take place among different regions is ignored. In this paper, we show how simple filtering procedures over different bands, applied to the resting-state fMRI signals, result in highly different connectivity matrices. Thus, it is highlighted that the functional network can be significantly dependent on the considered frequency range for the fMRI signal. This both justifies the need for a careful filtering of the signals, that avoids filtering out relevant frequencies, and also hints the possibility of classifying functional interactions according to the frequency where the connectivity among two areas is the strongest.**

***Index Terms*—Brain imagining; resting-state fMRI; signal processing in eHealth; network analysis; functional connectivity.**

I. Introduction

Over the last years, there has been a rapid surge in human neuroscientific research. This may also be due to the widespread availability of non-invasive techniques for measuring brain activity and structure, such as neuroimaging and electrophysiological recordings, producing large datasets of spatio-temporal data. It is generally accepted that the brain can be modeled as a complex network [1].

Brain network connectivity can be approached from many perspectives [2]. We focus on *functional connectivity* (FC), i.e., the analysis of how brain regions communicate to accomplish specific functions. This can be defined in terms of correlation between signals taken from different regions of interest (ROIs). Several electrophysiological and imaging techniques can be used to acquire these signals: functional magnetic resonance imaging (fMRI), among others, provides high spatial resolution, which is key to a reliable network description.

As many methods exist to describe communication channels [3]–[5], so happens for the representation of the connection between brain areas. The usual procedure is to compute cross-correlation between pairwise fMRI signals as a measure of synchronism, even among physically distant regions [6]. We focus, as done in the majority of the literature [7]–[9], on resting-state fMRI, i.e., signal measurements made from subjects at rest and not involved in any task, which is meant as a baseline connectivity state for the brain. Cross-correlation coefficients from the whole network can be collected to form the *FC matrix* that gives a snapshot representation of how different ROIs in the brain supposedly interact.

In most studies investigating FC, the signals of interests are considered within a fixed frequency band. Dependence of these signals on frequency is disregarded, in that both the frequency band is never discussed, and also the role of different frequency components within that band is not explored. We argue that, in this way, some aspects of the interactions among brain regions may go unnoticed [10], [11]. This would be the case if the synchronism phenomena depended on a specific timescale, and thus they were related to a specific range of frequencies of interest.

To explore this point in more depth, we investigate a *frequency-dependent* FC, that is, we systematically compute the FC from a resting-state fMRI dataset at different frequency bands, applying several filtering - with tunable parameters - and evaluating the impact on the connectivity matrix.

We can actually show that the FC matrix is heavily dependent on filtering, and therefore considering different frequency bands obtains remarkably diverse FC patterns. Thus, it makes sense to address a further research direction where brain network interactions are regarded in association with frequency aspects, e.g., we may account for faster or slower-paced interactions. From our preliminary results, we are also able to conjecture that, rather than being a fixed network structure where all the links are homogeneous, the human brain exhibits an extreme frequency diversity of interaction, as the presence of a functional connectivity links is approximately uniformly distributed across all frequencies. This kind of findings might lead to a richer modelling the brain network, possibly including frequency-differentiated interactions that discriminate brain links [12]. Such a characterization may in turn offer some better explanations of the healthy as well as the pathological brain activity.

The rest of this paper is organized as follows. In Section II we review the state-of-the-art about functional connectivity, and we also outline some related works that suggest that frequency differentiation may play a role in FC analysis based on fMRI. Section III discusses the methods used in this paper. We present the numerical results in Section IV, where we also highlight a quantitative analysis of the differences in functional connectivity matrices at different frequencies. Finally, in Section V we conclude the paper and discuss possible developments of the present analysis.

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II. Background

A. Functional Connectivity

FC has been widely studied with several electrophysiological and imaging techniques, ranging from local field potentials (LFP) to electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance (fMRI) [2].

In over twenty years of fMRI experiments, FC has been quantified both in healthy and in pathological conditions. Initially, FC was employed to explain the relationship between different areas of the brain during task-related activities. This long-time research activity led to the identification of several functional networks: the sensorimotor, visual, amygdala, and hippocampus, among others [13].

FC studies shed light on the pathological behavior of these networks in case of brain-related diseases, e.g., schizophrenia [14], major depressive syndrome [7], Alzheimer's disease [8], autism [11], as well as on changes in the normal healthy brain during development [15] and aging [16].

FC has been correlated with the so-called *structural connectivity* (SC): two regions that are physically connected (with significant SC values) usually show some degree of FC, too. Even more intriguingly, a vast body of works have shown significant functional coupling between areas that are not directly connected; this strongly unravelled the underlying network organization of the brain that can exploit indirect paths and dynamic clustering for communications between areas [17], [18].

Another measure is frequently associated with FC: the *effective connectivity* (EC) [19]. EC adds causality of the information flow between two areas where FC is established. FC and EC measures provide support, e.g., to stimulation and neuromodulation protocols targeting the normalization of a specific function, i.e., motor, cognitive or others.

Recently, increasing attention has been giving to the behavior of the brain and its oscillatory activity during the *resting-state*, i.e., the condition in which no task is required from the subjects except for relaxing while staying awake. In this case, no particular task-related response is expected; however, an undergoing *default-mode network* (DMN) [16] has been robustly identified. It seems to account for an *active-idling state* where the subject is doing nothing, but can be reactive to any external stimulus.

FC largely served to study DMN in many cases: particularly promising is the use of FC for the investigation of the DMN at resting state. This approach allows to dig into the functional segregated-integrated organization of the brain, whose subnetworks are functionally integrated through smaller FC values, giving rise to a complex *network-of-networks* [20], [21].

Quantitatively, FC can be computed in many ways: the correlation between time-series from pairs of ROIs has been firstly employed; then, other methods such as covariance and mutual information were exploited.

B. Related works

Some more recent works have hinted at the dependence of connectivity, especially meant as FC and EC, on frequency. In [6], the most interesting frequency bands were discussed, that can explain many neurophysiological human behaviours, from the ultra-slow frequencies (around 0.01 Hz) up to the ultra-fast oscillations (around 600 Hz). An inverse relationship was also pointed out between neural networks extension and frequency: high frequencies (i.e., short wavelengths) are usually confined in small neuronal areas, while low frequencies (i.e., longer wavelengths) are generally involved in the functioning of larger-scale networks.

Reasonably, the latter implies the time-varying characteristic of FC: specifically, studies on LFP, EEG and MEG made it possible to follow FC changes in time at frequencies in the broad range between 0.01 Hz up to 600 Hz. Nevertheless, among non-invasive neurophysiological techniques, EEG are known to be affected by low spatial resolution: therefore, fMRI has been also employed in the study of FC of the brain, despite its poor time resolution. However, fMRI cannot provide such high frequency information as given by MEG and EEG (and, invasively, by LFP). The typical time-course of FC based on fMRI is sampled over relatively short amount of times, of the order of tens of minutes, with the consequent possibility to only track very slow changes of the brain connectivity.

Recently, new studies are exploring the dynamic range of the fMRI signal [20] during resting-state, assumed to be a *steady-state*. The *chronnectome* model [22] has suggested the near-future direction and challenge of fMRI: time and frequency changes have to be tracked and quantified to unravel the spatial properties of "mutually informed activity" that is processed in the brain at any time, in any place.

Attempts in the same direction have been made also in the recent past by means of the decomposition of the fMRI signal in specific frequency bands related to physiology: 0.01–0.027 Hz (slow-5) and 0.027–0.073 Hz (slow-4) band [6] were considered in a study on resting-state FC to assess differences between normal subjects and a group of mild cognitive impaired patients [23]. Investigating on FC, the authors could suggest the involvement of a functional impairment rather than a structural difference in the amount of gray matter between the two groups.

Furthermore, the study of the five well-known functional brain networks mentioned above into the largest 0–0.24 Hz available frequency band showed a higher value of correlation of cortical networks in the range 0.01–0.06 Hz, whereas a limbic activity, i.e., deeper brain level, spread in the wider 0.01–0.14 Hz frequency range [13].

Finally, low frequency fluctuations (0.01–0.08 Hz) of resting-state fMRI signal were reported to reflect spontaneous neuronal activity [24]. Moreover, it is known that low frequency oscillations (0.01–0.073 Hz) can be detected in the gray matter, while relatively high frequency oscillations (0.073–0.25 Hz) are related to white matter [25].

III. Methodology

A. Dataset

We employed a dataset available at [26]. It was acquired using a SIEMENS TRIO 3-Tesla scanner in the Beijing Normal University Imaging Center for Brain Research from three subjects. During the experiment, they laid supine with

the head fixed by straps and pads to contain head motion. The subjects had to keep as motionless as possible and not to think systematically during the resting-state session.

The functional images were obtained using an EPI sequence with 33 axial slices, $3/0.6$ mm thickness/gap, 64×64 in-plane resolution, TR of 2 ms, TE of 30 ms, flip angle of 90 degrees, 200×200 mm FOV. Moreover, a T1-weighted sagittal 3-dimensional magnetization-prepared rapid gradient echo (MPRAGE) sequence is acquired covering the entire brain with the following parameters: 128 slices, TR of 2530 ms, TE of 3.39 ms, slice thickness of 1.33 mm, flip angle of 7 degrees, inversion time of 1100 ms, 256×256 mm FOV, and in-plane resolution of 256×192.

B. DPARSF toolbox

To analyze the data set, we employed Data Processing Assistant for Resting-State fMRI (DPARSF) [27], a MATLAB toolbox developed for pipeline data analysis of resting-state fMRI. This is an open source package based on some functions in Resting-State fMRI Data Analysis Toolkit (REST) and Statistical Parametric Mapping (SPM). We extracted signals from the Dosenbach's 160 ROIs [15] and computed the correlation matrix between each pair of them [28]. We also considered ideal low-pass and a high-pass filtering with a cutoff frequency (called β in both cases) being a tunable parameter, as further detailed in the next section.

C. Filtering

We processed our original fMRI data using low-pass and high-pass filters with different cutoff frequencies. Note that, since $TR = 2$ s, the sampling frequency F_s is 0.5 Hz; thus, in the frequency domain, the signals of interest can be found up to half that value. In particular, we referred as to $[0.01, 0.25]$ Hz as *full band*, since given the duration of our signals it is reasonable to ignore extremely low frequencies for functional interactions. We then considered several low-pass filtering of the input signal, actually limiting the signal in the band $[0.01, \beta]$ Hz, where, for our evaluations, parameter β is the independent variable taking different values. Similarly, we also considered a high-pass filtering in the band $[\beta, 0.25]$ Hz, again with tunable β.

IV. Numerical Evaluatons

A. Results

Considering Dosenbach's 160 ROIs, Fig. 1 shows the 160×160 FC matrix obtained considering the full band fMRI signal related to subject 3. Fig. 2 describes instead the FC matrix of the same subject 3, but after using a low-pass filter with cutoff frequency 0.05. This comparison immediately shows that the two matrices are quite different, which means that correlations between ROI pairs may significantly change if we consider signals filtered in different bands, and the overall holistic connectivity description is heavily influenced. In other words, considering the fMRI signals within different frequency bands produces different connectivity relationships between different areas of the brain. Thus, some functional links may

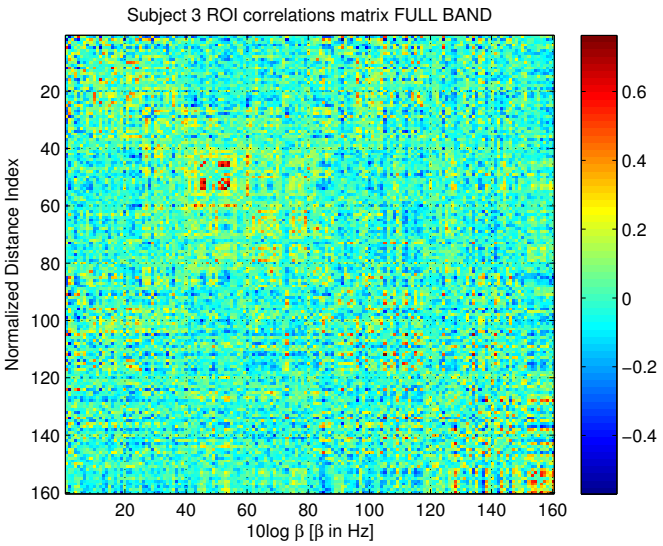

Fig. 1. Subject 3 FC matrix in the full band $[0.01, 0.25]$ Hz.

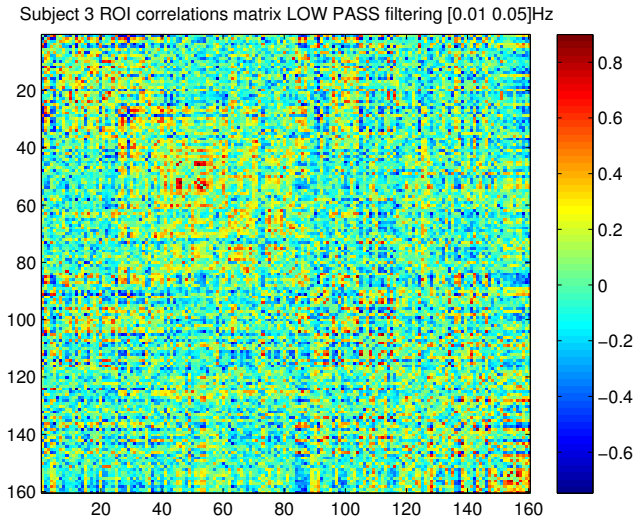

Fig. 2. Subject 3 FC matrix in the band $[0.01, 0.05]$ Hz.

or may not be present, and some links can even specifically appear stronger in a given frequency range.

To quantify the difference in FC for distinct bands, we use the following approach. We take the FC matrix for the full band, denoted as $\mathbf{R}_{(\mathrm{FB})}$, and the same FC matrix obtained from a further filtered version of the input signals with cutoff frequency β, which we call $\mathbf{R}(\beta)$; this can actually either be $\mathbf{R}_{\mathrm{LP}}(\beta)$ or $\mathbf{R}_{\mathrm{HP}}(\beta)$, depending on the filtering being low-pass or high-pass, respectively. Then, we compute the difference matrix $\Delta\mathbf{R}(\beta) = \mathbf{R}(\beta) - \mathbf{R}_{(\mathrm{FB})}$ that expresses the difference between the connectivity description obtained from the filtered signals and the original full-band signals. However, we need to quantify such a difference with a single parameter for representation purposes. To this end, we define a Normalized Distance Index NDI as

$$NDI = \frac{||\Delta\mathbf{R}(\beta)||_{\mathrm{F}}}{||\mathbf{R}_{(\mathrm{FB})}||_{\mathrm{F}}} \tag{1}$$

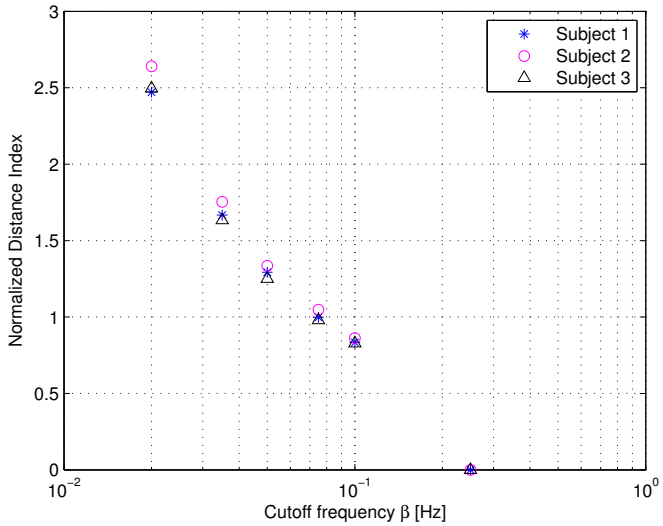

Fig. 3. Low-pass filtering: Normalized Distance Index between the FC matrices obtained in $[0.01, \beta]$ Hz and the full band.

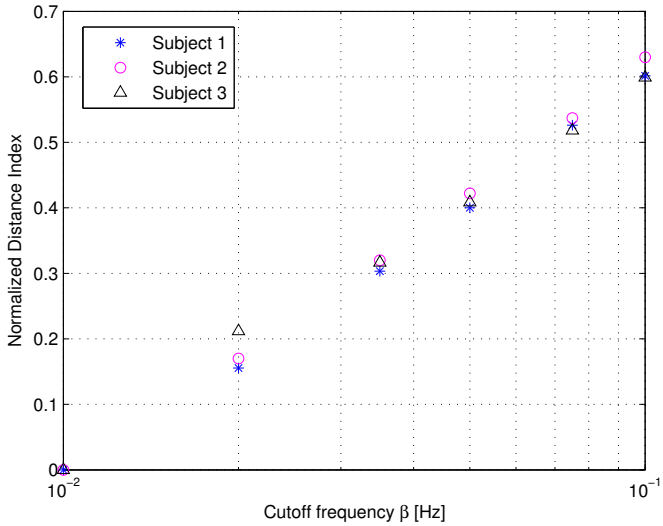

Fig. 4. High-pass filtering: Normalized Distance Index between the FC matrices obtained in $[\beta, 0.25]$ Hz and the full band.

where $||\cdot||_{\mathrm{F}}$ denotes the Frobenius norm operator. In other words, we consider the Frobenius norm among matrices as a measure of the diversity of the two FCs, and we normalize the result to the Frobenius norm of the original full-band matrix, to obtain a fair comparison. This value is meant to provides a basic quantification of the difference between the FC in the full band and that obtained from filtered signals. However, note that, while the NDI is normalized, correlation values of the FC can possibly be negative (and in certain cases even close to -1), and also the normalization factor, i.e., the Frobenius norm of the full band matrix, may be not too high. This implies that there might be cases where the NDI is larger than 1, which means that the matrices are significantly different.

Fig. 3 shows the results obtained for all subjects considering low-pass filtering, varying the value of the cutoff frequency β. First of all, it is possible to notice that the results are quite consistent, with extremely low inter-subject variability [5]. This seems to imply that the conclusions we have previously drawn for a specific subject are actually more general.

For low-pass filtering there are significant differences between the original FC in the full band and that obtained from filtered signals within a narrower band. As expected, the lower β the higher the NDI. However, strong differences in FC already show up when $\beta = 0.1$ Hz; when the cutoff frequency is further decreased, the value of the NDI goes above 1, a value so high that it implies a significantly different FC matrix. This may suggest that there are entirely separate connectivity phenomena, which become evident if only low-frequency interactions among brain regions are considered.

Fig. 4 considers instead a similar analysis, but for the case of high-pass filtering, with a tunable parameter β that still represents the cutoff frequency, so that, this time, the resulting passband is $[\beta, 0.25]$ Hz. Again, we plot NDI versus β and the results are analogous to those of Fig. 3: for example, there is a strong consistency of the results across different subjects. Also, the narrower the considered bandwidth, the higher the NDI. However, the maximum value is smaller than before; actually, the NDI is below 1 for all the cases considered, which seems to suggest that a intra-region FC has a limited activity for lower frequencies.

Combining the observations from both plots, we can infer that connectivity phenomena are significantly different at lower and higher frequencies, to the point that they can be seen as almost unrelated trends, possibly coming from separate physiological aspects. While most of the FC relationship is captured if signals are filtered with sufficiently large passband, just considering the full band may lead to hiding some existing correlation trends that are relevant at certain sub-bands.

Remarkably, for the purpose of being systematic, our analysis focuses on a variable β without searching for any specific physiological correlate. It may be worth considering specific frequency bands, with a precise physiological role: this kind of investigation, which is left for future work, may give an even better explanation of the differences across frequencies.

B. Discussion

To get a dataset of signals that are usable within a toolbox, several pre-processing procedures are required, most of the times including a filtering to limit the signals within a proper frequency band. The resulting "polished" signals feed the toolbox so as to achieve a quantification of FC (or any similar metric). So, a first immediate conclusion of our study is that this preprocessing on the signals requires special care, in particular it must be done avoiding filtering out some relevant frequencies, as this can strongly affect the conclusions on the undergoing physiological phenomena that the researcher desires to observe.

Moreover, it is worth noting that some other options, e.g., avoiding head motion correction or similar adjustments on the signals, may definitely play a role here. We verified that changes in the pre-processing pipeline lead to slightly different FC matrices and thus change the punctual values of NDI;

however, the bulk of our conclusions, i.e., that the holistic representation of the FC matrix heavily changes at different frequencies, still holds true.

Beyond the importance of a correct pre-processing of fMRI signals, our analysis can also motivate the efforts towards gaining a systematic understanding of the role played by frequency components with respect to functional connectivity. The most striking aspect of our evaluation graphs is that, apparently, a linear relationship exists in the presence of links (i.e., what represented by the NDI) and the width of the considered frequency band.

Should this trend be confirmed, a distribution law of functional connections in the brain across different frequencies may be estimated. This aspect, if ultimately proven, would be extremely suggestive in implying that functional connectivity is not a static property of the brain, but rather is variegate and describes a plethora of different functions that are themselves frequency-dependent. An in-depth discussion of these features may therefore suggest interesting implications from signal processing to physiology that can open up further contributions in the fields of neurosciences.

V. Conclusions and Future Work

We considered the functional structure of the human brain and its areas, seen as a network of connections. Connectivity is usually related via correlation among physiological signals (such as resting-state fMRI). Our investigation centered around the role of spectral components of these physiological signals, and whether this may hinder a practical meaning.

We definitely found a relevant frequency diversity of fMRI signals, that ought to be included in the analysis when discussing functional connectivity. One way of doing that may be the definition of a *multi-dimensional* FC in which also the frequency component plays a role. Brain regions may be connected differently, according to the band where the resting-state fMRI, or any other physiological signal, are considered, and therefore multiple matrices can be obtained. In this context, it may be worth repeating our analysis, instead of performing a general parametric analysis, by concentrating on specific frequency bands such as those with known biological meaning [6], [13].

Another related way of accounting for this dependence on frequency is to describe the links among the brain regions with spectral parameters. For example, a connection between regions may be associated with the frequency where the FC value is strongest and/or a proper passband where most of the interactions take place. Also, it may be relevant to investigate the span of these frequencies and their possible concentration around some specific values [29]. We were unable to identify privileged frequency ranges, which may also suggest that a healthy human brain has interactions evenly distributed across the entire frequency span. It would be relevant to systematically describe a reference distribution on a wider dataset and possibly compare healthy and pathological subjects.

These characterizations may be extremely useful to get a richer description of the brain as a complex network, and ultimately lead to a better understanding of neural phenomena as an of investigation and a challenge for future research.

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