Multifractal dynamics of resting-state brain functional connectivity

Doctoral theses

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Introduction

The brain forms a complex system in its anatomical structure as well as its functional organization. This system is composed of relatively simple elements, however due to their interactions it becomes able to perform higher-level functions as well. On this basis, in recent decades the investigation of how different regions of the brain interact recieved ever increasing attention. *Functional connectivity* (FC) studies – aimed at describing and understanding connection patterns, networks and principles of organization in the brain – became one of the leading fields of neural science in a short period of time.

Several approaches from many fields of research can be utilized when analyzing functional connectivity. One of the most widely used among those is the network theory approach that considers the brain as a network, where nodes represent regions of the brain while links represent the functional interactions, connections between them. These networks than can be characterized quantitatively through several network measures, which describe different topological aspects of the given network.

Until recently, most FC studies followed a ’static approach’, implicitly assuming that functional connections (and

thus functional networks) of the brain are time invariant i.e. stationary. A dynamc aprroach, however – that takes into account the fluctuating/intermitting nature of functional cooperation between neuronal populations – could provide a more detailed and probably more realistic description of brain function. Studies of the latter kind investigating the *dynamic functional connectivity* (DFC) of the brain shifted into focus only recently, when several studies confirmed the fluctuating (instead of stationary) nature FC even in the resting state. Utilizing a dynamic network theory approach to investigate DFC would allow for monitoring the temporal evolution of functional brain network topology, thus yielding a description of the spatio-temporal dynamics of the brain as a complex system.

Several physiological processes – such as heart rate variability, ion channel kinetics or resting-state neural activity – were shown to express scale-free (*fractal*) dynamics. Such processes do not have a characteristic timescale, instead their statistical properties follow a power-law relationship with respect of the scale of observation. For several processes – including neural dynamics – the scaling itself can vary in time yielding

multifractal (MF) dynamics. In this case the scaling cannot be captured in a single but a set of scaling exponents.

Previous studies, using methods other than dynamic graph theoretical analysis demonstrated the scale-free nature of DFC. Nonetheless, most DFC studies focus on a more detailed, time-dependent description of network topology – e.g. identifying reoccurring, characteristic connectivity states – while the dynamics itself is characterized through simple second order statistical measures as the standard deviation. Therefore, these studies disregard the known scale-free and possible multifractal nature of DFC. Verifying the true multifractal nature of DFC would not only reveal a previously unknown aspect of brain function but it could provide potential new biomarkers for clinical studies in the future.

Objectives

Although previous studies demonstrated the scale-free (monofractal) nature of DFC, these studies either i) ignored its potential multifractality, or ii) with the applied methodology the fluctuations of DFC appeared as strictly monofractal. A dynamic graph theoretical approach provides a simple, yet robust tool for monitoring and investigating DFC. Therefore, I set the following goals for my PhD studies:

- Creating a dynamic graph theoretical analysis framework in order to investigate the possible multifractal nature of DFC.
- Verify the true multifractal nature of DFC.
- Compare different topological aspects of dynamic brain networks based on their (multi)fractal properties.
- Verify the true multifractal nature of individual dynamic functional connections between various brain regions.
- Explore, if individual functional connections show any particular spatial distribution over the cortex in their (multi)fractal properties.

Materials and methods

Data acquisition, subjects, experimental paradigms

In our first study 13 young, healthy volunteers (mean age 23±2 yrs., 7 female) participated. Resting-state neural activity of the prefrontal cortex (PFC) was monitored for 20 minutes using functional near-infrared spectroscopy (fNIRS). The fNIRS system allowed for a 3Hz temporal resolution over 16 regions of the PFC. In our second study 24 young, healthy volunteers (mean age 24±2 yrs., 12 female) participated. We performed resting-state electroencephalography (EEG) measurements for 5-5 minutes in eyes open and eyes closed states. Measurements were carried out using a commercial Emotiv Epoc+ system (Emotiv Systems Inc., San Francisco, CA, USA). The device had a sampling frequency of 128Hz and it allowed for monitoring neural activity of 14 regions of the whole cortex according to the international 10-20 system. Both studies were approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics and all subjects provided written informed consent prior to measurement.

Data preprocessing

First- and second-order trends were removed from raw fNIRS signals. Then, a band-pass filter with cutoff frequencies of 0,01 and 0,1Hz was applied to remove systemic periodic components. Finally, correlation based signal improvement (CBSI) was applied to simultaneously eliminate motion artefacts while also separate a signal component related more closely to neural activity. All subsequent analysis steps were done on total hemoglobin (HbT) signals acquired as the sum of oxygenated and deoxygenated hemoglobin concentrations.

Raw EEG signals were preprocessed using the freely available EEGLAB toolbox. Artefacts related to eye movement, blinking or other sources (e.g. muscle contraction) were removed using independent component analysis (ICA), then the data was band-pass filtered to the traditional frequency bands used in EEG analysis (delta, theta, alpha, beta and gamma). All subsequent analysis steps were performed for all frequency bands as well as broadband EEG data.

Dynamic functional connectivity analysis

Sliding window correlation (SWC) analysis was performed on preprocessed fNIRS data. In that, a time window (with the width

of 30, 45, 60, 75 and 90s) was shifted along the signal and for every time point, the Pearson correlation coefficient for all possible pairs of channels were calculated. The resulting connection matrices – that define a weighted, undirected dynamic network – were thresholded (using several values between 0,05 and 0,7) to exclude weak, non-significant connections. Finally, for every time point the actual topology of the network was characterized through three different network measures (see below), yielding the network metric time series capturing the spatio-temporal dynamics of the PFC.

DFC analysis of EEG data was done using the Synchronization Likelihood (SL) method that captures the degree of synchronization between two temporal processes in a time resolved manner. SL is ideal for EEG analysis as it is able to identify non-linear relationships while it is not affected by the non-stationarity of the signals. Starting parameters of SL were tuned to match each frequency band. SL time series were calculated for all possible combinations of the channels and sorted into a dynamic connection matrix. Subsequently, network measures were calculated for every time point, similarly to our fNIRS study.

In both studies, three network measures were used to characterize network topology, namely Density (D), Clustering coefficient (C) and Efficiency (E). Each of these captures a different, important aspect of network topology. Moreover, in our second study the SL time series – capturing the dynamics of individual functional connections between brain regions – were also made subject to further analysis.

Multifractal time series analysis

Multifractal properties of network metric time series and SL time series were estimated using focus-based multifractal signal summation conversion (FMF-SSC) method. During FMF-SSC analysis the standard deviation (σ) of the process is calculated along a set of different scales (s) as well as generalized statistical moments (q), yielding the unified scaling function, $S_\sigma(q,s) = \left\{\frac{1}{N_s}\sum_{v=1}^{N_s}\{\sigma(v,s)\}^q\right\}^{1/q}$. The generailzed Hurst exponent, $H(q)$ for every q can be estimated form $S_\sigma(q,s)$ with linear regression. In monofractal signals $H(q)$ is independent from q, while in the case of multifractality values of $H(q)$ decrease monotonously with increasing q. Multifractal properties of the dynamic functional networks and individual connections were

characterized with two end-point parameters, namely i) $H(2)$, that is the monofractal scaling exponent, which captures global scaling and ii) $\Delta H15$, that is the difference between the $H(q)$ values acquired at a minimal ($q_{min} = -15$) and a maximal ($q_{max} = 15$) moment thus capturing the degree of multifractality (which for monofractal signals $\Delta H15 \cong 0$). Starting parameters of the FMF-SSC method (s_{min} and s_{max}, range of q, number of different scales) were set according to the length and sampling rate of each time series.

Statistical testing for true multifractality

True multifractality of the time series were tested against appropriately generated surrogate datasets in three aspects:

1. Global power-law scaling. Presence of sacale-invariance was verified through the power spectrum. In that, goodness-of-fit statistics of a power-law function on the spectrum of the original signals were compared to those acquired from data generated with known power-law spectra.

2. Multifractality due to long-range correlations. Presence of long-range correlations were verified through shuffling the values of the original time series. If the repeated FMF-SSC analysis of

shuffled data yielded $H(q) \cong 0{,}5$ (white noise), the previously observed multifractality was considered as a consequence of long-range correlations.

3. Verifying true multifractality. $\Delta H15$ values of the original time series were compared to those acquired from similar, but strictly monofractally generated signals, excluding the possibility of multifractal background noise.

Statistical analysis

In our first study, true multifractal nature of the network metrics time series was verified through the three-step testing framework described above. MF properties of the different network measures were compared using repeated measures ANOVA. The possible effect of window size used in SWC analysis was also investigated using repeated measures ANOVA.

In our second study, true multifractality of network metric time series and SL time series was verified using the same testing framework as previously described. MF properties of dynamic networks were compared using two-way repeated measures ANOVA, taking into account the possible effect of state (eyes open/closed), gender (male/female) and network measure (D, C

and E). Spatial distribution of individual connections based on their multifractal properties were plotted as a network after standardization and described qualitatively. The spatial correlation between $H(2)$ and $\Delta H15$ was also calculated.

Results

Multifractal DFC in the prefrontal cortex

Over 91% of the Density and Clustering coefficient time series passed all three tests and qualified as true multifractals when analyzing DFC with 60s time window. This fraction was still over 82% when analyzing the Efficiency time series. Similar results were obtained using different window sizes, therefore it could be stated that DFC of the prefrontal cortex express true multifractal dynamic in the vast majority of the cases.

Differences between network measures

$H(2)$ and $\Delta H15$ values of D, C and E time series showed a characteristic difference, in that MF parameters of C were significantly smaller than those of D and E ($H_D(2) > H_C(2) < H_E(2)$ and $\Delta H_D15 > \Delta H_C15 < \Delta H_E15$). This pattern appeard independently of the threshold applied during DFC analysis.

Effect of window size on multifractal parameters

Both $H(2)$ and $\Delta H15$ of all three network measures increased with the applied window size, however the characteristic difference observed at 60s window size (D > C < E) persisted. It has to be noted that over 75s window size we found a saturation of both $H(2)$ and $\Delta H15$.

Multifractal DFC in the whole cortex

We found a similarly high fraction (over 90%) of true multifractal time series when investigating DFC over the whole cortex with EEG. Similar results were found in all frequency bands, regardless of network measure, state and gender.

Effect of network measure, state and gender

Results similar to those found in our first study were found regarding the effect of network measure on $H(2)$ ($H_D(2) > H_C(2) < H_E(2)$) in all frequency band. When investigating $\Delta H15$, this charateristic difference only occurred in the delta band. We found significantly higher $H(2)$ values during eyes closed state in the alpha and beta bands, nevertheless the state had no effect on $\Delta H15$. Effect of gender was mostly tendential, with higher values in the male group for both MF measures.

Multifractal dynamics of individual connections

Over 90% of connections were found to be true multifractals in the delta, theta and alpha bands, however this fraction was found slightly lower in the higher frequency bands as well as for broadband EEG.

Topology of connections regarding their MF properties

Higher $H(2)$ values were generally found in connections linking spatially and functionally proximal regions of the brain. This could be observed the most prominently in the frontal and prefrontal regions, where highest $H(2)$ values were found. A similar topology appeard when investigating $\Delta H15$ of the connections except for the delta band, where basically the opposite results occurred. In that, the highest $\Delta H15$ values were found in connections between distant regions such as the frontal regions and the occipital cortex. Investigating the spatial correlation of $H(2)$ and $\Delta H15$ therefore we found a strong anticorrelation in the delta band, while strong positive correlation in the rest of the frequency bands. In case of broadband EEG data the two multifractal parameters were independent.

Conclusions

Multifractal nature of dynamic functional connectivity

In our studies we found that resting-state dynamic functional connectivity of the brain (in the vast majority of cases) expresses multifractal dynamics. We demonstrated this phenomenon in the prefrontal cortex and with whole-brain measurements as well, with two fundamentally different imaging techniques. Moreover, similarly high fraction true multifractality was found in all cases regardless of subjective parameters (window size, threshold, frequency band). Thus, based on our results it can be reasonably assumed that multifractal dynamics is indeed a fundamental property of DFC.

Strong multifractality occured when investigating the dynamics of individual functional connections instead of global network topology. Fraction of true multifractality was the highest in the delta, theta and alpha bands, while this fraction was slightly lower in the higher frequency bands. It is important to note however, that the sampling frequency of the EEG device used in the study allowed only for an imperfect reconstruction during SL analysis in these frequency bands, therefore the possible implementation of these results is certainly limited. Nevertheless

it could be concluded that dynamic functional networks of the brain – those global topology fluctuates according to MF dynamics – are constructed from connections that express true multifractal dynamics themselves.

Multifractal properties of global network measures

Investigating DFC in the prefrontal cortex we found that different global network topological measures expressed different MF characteristics. Comparing the MF parameters of D, C and E we found a characteristic pattern. In that, global (as captured in $H(2)$) and the variability of scaling property (as captured in $\Delta H15$) of Clustering coefficient – describing network segregation – could be characterized with lower values than those of Density and Efficiency – capturing network wiring cost and integration, respectively. This tendency was found the same in whole-brain measurements regarding $H(2)$ in all frequency bands, however the same difference was found only in the delta band (0,5-4Hz) when investigating $\Delta H15$. Measurements performed over the PFC were also filtered to a low-frequency (0,01-0,1Hz) range, therefore it is possible that differences found in the degree of multifractality are only characteristic for low-frequency neural activity. The higher $H(2)$ values found in the alpha and beta

bands during eyes closed state were also demonstrated (for a density-like measure) in an earlier study. Therefore our results are consistent with previous findings in the literature, extending their validity to other aspects of network topology as well (segregation and integration).

Our results suggest that the brain presents itself as a complex system where global and local information processing can be characterized with different levels of complexity. This is well in line with previous observations where large-scale (global) neural activity could be characterized with scale-free ($(1/f^{\beta}$-like) dynamics, while locally the activity of neuronal populations became even more synchronized.

Finally, the scale-free nautre of global connectivity dynamics can indicate a possible self-organized critical (SOC) state behind resting-state brain function. To further extend on this we investigated the waiting times between similar connectivity states and found that these show an exponential distribution. The dynamic connection network of the brain therefore bears two fundamental properties of critical systems – scale-free dynamics and an exponential distribution of waiting times between events

–, thus our results support the hypothesis that the brain is in a possible self-organized critical state in the resting state.

Multifractal dynamics of individual connections

Investigating the spatial distribution in the MF parameters of individual connections we found a characteristic topology, where strongly autocorrelated connections (i.e. with high $H(2)$) were found mostly in the frontal and prefrontal areas, while connections with lower autocorrelation were found between anatomically and functionally distant regions. A similar topology appeared when investigating the degree of multifractality in all frequency bands except for delta, where an opposite pattern occurred. Investigating the dependence of the two parameters – that is indeed not trivial, as they describe two independent property of (multi)fractality – we found strong correlation (or in the delta band, strong anticorrelation). Based on the results of an *in silico* simulation we performed in one of our previous studies, the positive correlation found between $H(2)$ and $\Delta H15$ suggests that the self-organized critical nature can not only be captured in global network dynamics, but in individual connections as well. Moreover, in case of strong correlation between $H(2)$ and $\Delta H15$, higher values are produced by larger SOC systems. This is further

supported by the fact that $H(2)$ values represent the relative dominance of slow oscillations, that can only produced by larger neuronal populations. On this basis our results are well grounded from a physiological perspective as well, as the highest $H(2)$ and $\Delta H15$ values were found in the prefrontal and frontal areas, that is known as the highest level association cortex and is very densely connected both anatomically and functionally, making it able to perform higher-order functions. Implementing results found in the delta band requires further investigation.

In summary, based on the results of the two studies described previously I could draw the following conclusions:

- The dynamic functional connectivity of the prefrontal cortex expresses true multifractal spatio-temporal dynamics as captured in global network measures, namely Density, Clustering coefficient and Efficiency.
- Various topological aspects of the functional network of the PFC – as captured in D, C and E – can be characterized with different multifractal properties.
- The dynamic connection network of the PFC shows the characteristics of a self-organized critical system.

- DFC express true multifractal dynamics not only in the PFC but over the whole cortex as demonstrated by EEG measurements.
- The difference in MF characteristics found between various network topological aspects in the PFC appeared similar in networks of the whole cortex.
- In the alpha and beta bands, DFC can be characterized with higher $H(2)$ values of D, C and E during eyes closed state.
- Individual connections linking various regions of the brain show not only mono-, but indeed true multifractal nature. This property holds especially well for connections of the lower frequency bands (delta, theta and alpha).
- Individual functional connections show a characteristic topology in their multifractal properties.

List of publications

Publications related to the theme of the PhD thesis:

- **Racz, F.S.**, Mukli, P., Nagy, Z., and Eke, A. (2018) Multifractal dynamics of resting-state functional connectivity in the prefrontal cortex. *Physiol Meas*. IF: 2,006
- **Racz, F.S.**, Stylianou, O., Mukli, P., Eke, A. (2018) Multifractal dynamic functional connectivity in the resting-state brain. *Front Physiol* 9. IF: 3,394

Publications unrelated to the PhD thesis:

- **Racz, F.S.**, Mukli, P., Nagy, Z., and Eke, A. (2017) Increased prefrontal cortex connectivity during cognitive challenge assessed by fNIRS imaging. *Biomed Opt Express* 8(8)**,** 3842-3855. IF: 3,344
- Mukli, P., Nagy, Z., **Racz, F.S.**, Herman, P., Eke, A. (2018) Impact of Healthy Aging on Multifractal Hemodynamic Fluctuations in the Human Prefrontal Cortex. *Frontiers in Physiology* 9. IF: 3,394