SCALE-FREE FUNCTIONAL CONNECTIVITY OF BRAIN NETWORKS REVEALED BY ELECTROENCEPHALOGRAPHY

Ph.D. theses

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1. Introduction

Signatures of brain activity are readily captured in neuroimaging records. However, the limited ability to establish inference from neurophysiological processes to behavior and cognition in humans has been a significant challenge in neuroscience. Investigating brain networks could provide a link between these levels of mental activity as the connections between different brain regions are the foundation of higher brain function and are also characteristic of the resting-state. A common approach to describing these networks in human studies is estimating functional connectivity (FC) FC from functional brain imaging data.

A standard method of examining brain function with high spatial resolution is functional magnetic resonance imaging (fMRI), which can detect the impact of mental workload and various neuropsychiatric diseases on FC. A cost-effective alternative to fMRI is electroencephalography (EEG), which is primarily suitable for regional assessment of the electric changes in the brain cortex and has orders of magnitude higher temporal resolution (sampling rate). Most studies have focused on the narrowband (oscillatory) component of electrical activity, usually classified in 5 bands (delta: 0.5-4 Hz, theta: 4-7 3 Hz, alpha: 7-14 Hz, beta: 14-30 Hz and gamma: 30-60 Hz). However, the non-oscillatory component of EEG spanning abroad range of frequencies also bears a fundamental physiological role.

While the ability of EEG to capture local field potential fluctuations evoked by mental strain in a single brain region has been recognized since its invention, multichannel recordings could provide a large-scale assessment of spatiotemporal organization of neural dynamics during task. Thus, in addition to the study of single time series (univariate analysis) of brain activity, the investigation of the relationship between pairs of time series (bivariate analysis) began. FC captures the coordinated action of distinct brain regions extending the structural connectivity formed by the axonal network of directly interconnected neuronal assemblies. Conversely, the functional connection between two time series can be estimated by their statistical interdependence. Based on this principle, a new direction in neuroscientific research developed, whose approach is to construct the FC of the human brain and find how it relates to cognitive functions. A brain network can be constructed as a constellation of nodes interconnected by edges. The nodes of the network represent the different brain regions, while the edges are the functional links between them. Using graph theory, scientists can distill the information about the network's architecture. For example, it has been found that the normal healthy brain follows a small-world network organization. According to this, most cortical areas are sparsely interconnected, while a small number of hub regions are responsible for the linkage between these functionally distant areas. The hub regions seem fundamental for normal brain function since disruption of hub regions and small-world architecture have been linked with clinical conditions like coma, Alzheimer's disease, and schizophrenia. The density of these small-world networks seems to be governed by scale-free dynamics.

The scale-free (or fractal) brain dynamics are ubiquitous, and it appears as the broadband (non-oscillatory) component of EEG. Mathematically, a scale-free property emerges in the power-law relationship between a measure (Ω) of the process and its scale (s): $\Omega \propto s^{\lambda}$. It is then easily understood that Ω's ratio in two different scales is influenced only by the relative scale and not their explicit values: $\frac{X1}{X2} = \left(\frac{s1}{s2}\right)^{\lambda}$, hence the term "scale-free" is coined for the process. One example of scale-free brain dynamics is the $1/f$ noise of the EEG's power spectrum, where the power density (P) is related to the frequency (f) in a power-law manner ($P = f^{\lambda}$). The superposition of oscillatory neural activity appears as narrow range peaks representing the traditional EEG bands (e.g. 10 Hz activity giving rise to the alpha peak). While the oscillatory components of EEG received more attention due to the characteristic time scales of neurophysiological processes, the broadband fractal component was believed to be noise, hence "1/f noise". The significance of this component lies in the characteristic differences found by comparing rest and task states during object recognition or schizophrenic patients with age-matched healthy controls. A large fraction of the corresponding EEG changes is ascribed to the altered fractal profile of the signal. Thus, a great wealth of information can be revealed by scale-free analysis of EEG records relevant to cognitive and clinical neuroscience.

So far, only the scale-free properties of the univariate EEG signals have been studied extensively; on the other hand, the scale-free coupled dynamics of EEG tracings have remained hidden. The aforementioned power-law relationship can be found in the coupled dynamics as well (e.g. power-law relationship of power cross-spectrum), suggesting that the fractal nature of FC could be of interest for physiological studies of human brain function. Fractal FC indicates the existence of coupling that persists through time, in contrast to the fast-decaying FC captured by traditional methods. Moreover, fractal formalism has been extended to multifractality, where more complex interactions of this time-persisting FC can be studied.

Even though the resting-state studies have dominated the field, more and more scientists have begun to explore the change of FC during mental strain. Such FC was studied earlier by our research group, who showed that the interconnectivity of the prefrontal cortex increases during visual pattern recognition VPR). Various estimators of FC have been introduced to assess task-related differences in statistical interdependencies between simultaneous neurophysiological processes recorded from different localizations. A common feature of these analyses is that they are typically restricted to a single time scale, which neglects the scale-free characteristics of neural dynamics. The previously introduced bivariate multifractal analysis can overcome this limitation and assess the task-dependent change of scale-free FC during a VPR task.

2. Objectives

Although scale-free coupling of the brain regions has been recognized, only monofractal tools have been used for its assessment, despite the multifractal features of FC. The research underlying this dissertation aims to investigate the multifractal aspect of FC using the already-introduced bivariate focus-based multifractal (BFMF) analysis. To evaluate the presence of scale-free coupled dynamics, we devised a new battery of bivariate multifractality assessment tests. BFMF analysis and subsequent assessment of FC were performed in two different sample populations and experimental protocols. The objective of the first study was to validate BFMF as a viable FC estimator. Brain network topologies were reconstructed from BFMF measures estimated from an online dataset of resting-state eyes-closed (EC) EEG recordings. The variability between different subjects and across brain regions was evaluated to assess the determinants of multifractal FC. The second study targeted the reorganization of multifractal FC during a VPR task of stratified difficulty compared to resting states. We also aimed to determine the association between cognitive performance metrics and EEG-based measures of brain network topology.

3. Methods

Bivariate focus-based multifractal analysis
A common step in multifractal analysis in the time domain is to obtain a scaling function (S) which reveals the relationship between the time scale (s) and a scale-dependent measure for a signal of length L. In the bivariate case the measure (covariance) is calculated for a pair of time series (X, Y) yielding $S_{XY}(q,s) = \left(\frac{1}{N_s}\sum_{v=1}^{N_s}|cov_{XY}(v,s)|^q\right)^{1/q}$. Generalized Hurst exponent function consists of scale-free exponents describing the power-law relationship between time scale and covariance, a key feature of fractal processes. Although bivariate $H(q)$ can be estimated for each statistical moment (q) separately, we used an enhanced multifractal formalism introduced earlier by our research group. In that, a focus point [ln(L), ln$S$(L)] is incorporated in the regression model fitted to S_{XY}, which allows for the simultaneous assessment of $H(q)$ for all q values: $\ln S(q,s) = H(q)\cdot[\ln(s)-\ln(L)]$. The final output of BFMF is the bivariate $H(2)$ and ΔH_{15}. Bivariate $H(2)$ signifies the degree of long-term cross-correlation, while bivariate ΔH_{15} reflects the degree of multifractality between the recorded physiological processes. However, the bivariate multifractal model might not be appropriate to capture the long-

term cross-correlation and coupled non-linear dynamics. In addition, the error of estimates due to the finite size effect (discrete signals of finite length) can also lead to false conclusions regarding the true physiological origin of signals. Our newly developed multifractality assessment tests investigated: *i*) power-law relationship in both frequency and time domain *ii*) multifractality emerging through non-linear dynamics *iii*) distribution-type multifractality and *iv*) genuine nature of bivariate multifractality

Validation of BFMF in resting-state

An online dataset of 12 young, healthy volunteers was investigated during 5 minutes of eyes-closed resting state. About 33 seconds (2^{14} datapoints) of artifact-free, preprocessed signals were analyzed per subject. To reduce the dimensionality of our data, the 62 channels were grouped in 6 resting-state networks RSNs): default mode, frontoparietal, visual, somatomotor, dorsal attention, ventral attention and limbic networks. The BFMF-derived values of the connections were averaged, resulting in within-RSNs and 15 between-RSNs values for each of the bivariate $H(2)$ and ΔH_{15} networks.

Reorganization of multifractal FC during VPR

58 young, healthy volunteers participated after giving informed consent. The experiment consisted of 3 minutes eyes-closed (EC) resting-state, followed by 3 minutes of eyes-open (EO) resting-state. The resting-states preceded 30 trials of a VPR task, divided equally into 3 difficulty levels (Easy, Medium and Hard). In total 48 segments per subject were analyzed (9 EC, 9 EO, 10 Easy, 10 Medium and 10 Hard). The bivariate $H(2)$ and ΔH_{15} values for the same state were averaged, ending up with 5 segments (EC, EO, Easy, Medium, Hard) for every BFMF-derived network [bivariate $H(2)$ and ΔH_{15}]. To characterize the obtained networks, we calculated D^W (sum of connection strength of every connection passing from the node) and $\overline{D^W}$ (average of all D^W), using either bivariate $H(2)$ or ΔH_{15} as weights of edges reflecting the strength of scale-free coupling.

Statistical Analysis

After assessing normal distributions with Lilliefors test, we used the Friedman test followed by post-hoc pairwise tests. False discovery rate was controlled by the Benjamini-Hochberg method. The concordance between subjects was assessed via Kendall's coefficient, while Spearman's coefficient captured the relationship between cognitive and FC parameters.

4. Results

Most of the connections showed true multifractal character for both rest and task states. Both experiments found significant negative correlations between the bivariate $H(2)$ and ΔH_{15} in both experiments. The localization of scale-free FC varied the most in the $H(2)$ networks in the first study (**Figure 1**), while the opposite was observed in the second study (**Figure 2**). The two studies also differed in the subject concordance of the bivariate $H(2)$ and ΔH_{15} values. The resting-state study revealed strong subject agreement, while only a small concordance was found in the ΔH_{15} networks of the VPR study. During VPR the FC increased, but the task's difficulty did not influence the brain network reorganization (**Figure 3,4**). The success rate (SR) comparisons revealed significant differences, with the Hard task being the least successful (**Figure 5**). In the reaction time (RT) investigation, we found that the lowest RT was recorded in the Easy, followed by the Medium and finally the Hard trials, which took the longest to solve (**Figure 5**). Additionally, significant positive correlations were observed between the $\overline{D^W}$ and RT of the Easy and Hard states of ΔH_{15} networks (**Figure 6**).

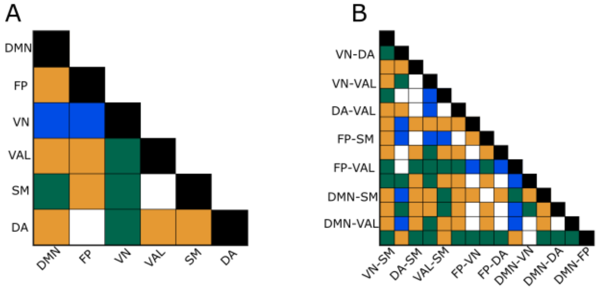

Figure 1: *Effect of regional variability*. Significance of connection-to-connection comparisons of within- (Panel A) and between- (Panel B) RSNs after the appropriate correction for bivariate H(2) and ΔH_{15}. Blue: Only ΔH_{15} comparison test was significant. Orange: Only H(2) comparison test was significant. Green: Both H(2) and ΔH_{15} comparison tests were significant.

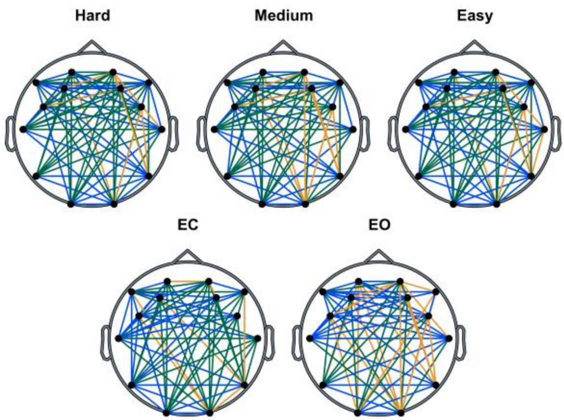

Figure 2*: State-dependent paired comparisons of the node degrees of different brain regions*. The edge color corresponds to the significance of the comparison between the two nodes of the edge. Orange: only $H(2)$ network comparison was significant, Blue: only ΔH_{15} network comparison was significant, Green: both $H(2)$ and ΔH_{15} networks comparisons were significant.

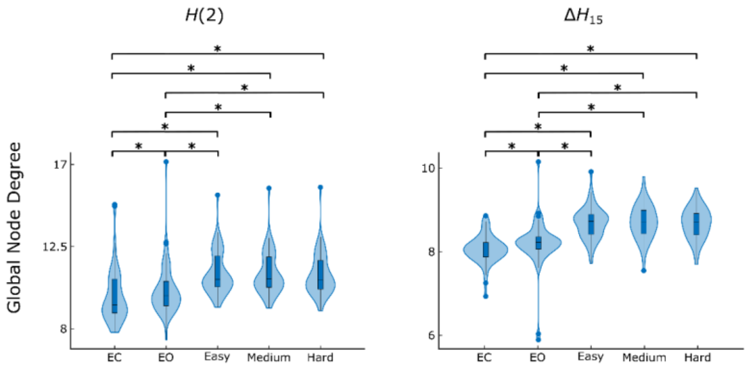

***Figure 3**: State-dependent weighted global node degree distribution of H(2) and ΔH_{15} brain networks*. Significance marked by *.

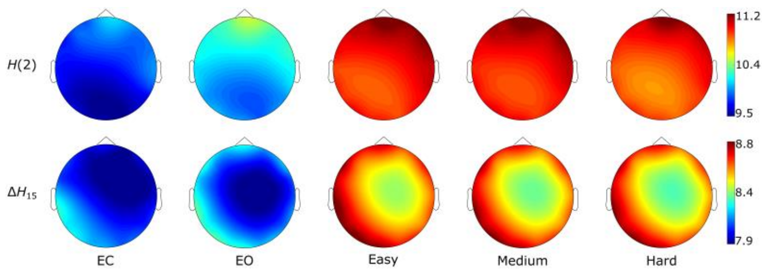

***Figure 4:** State-dependent weighted node degree topology of H(2) and ΔH_{15} brain networks*. The color bars represent the values of the local node degrees.

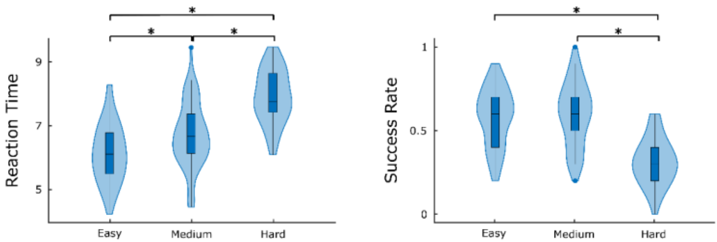

Figure 5*: Average success rate and reaction time for different difficulty levels.* Significant differences are marked by *.

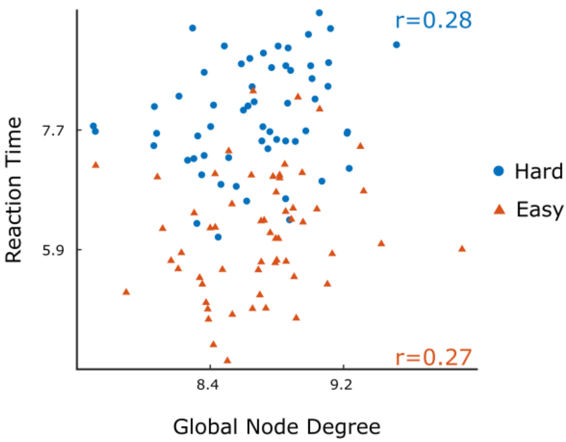

Figure 6*: Scatter plots of the reaction time vs global node degree for Easy (orange) and Hard (blue) task in ΔH_{15} networks and their Spearman's correlation (r).*

5. Conclusions

- **Several scale-free connections in rest and task**

According to the concept of self-organized criticality, scale-free systems are at the edge of order and chaos, where small perturbations can have major repercussions. This balance is achieved by intrinsic control parameters. A possible candidate for this control parameter is the excitatory and inhibitory feedback loops of the brain's circuitry. In the last few years, different teams have shown that disturbance of the balance between excitatory and inhibitory stimuli can lead to deviations from criticality. The negative correlations found between $H(2)$ and ΔH_{15} indicate that the two scale-free properties (long-term cross-correlation and degree of multifractality) should be studied in tandem and that using only one of them would not give us complete insight into the fractal brain dynamics.

- **Scale-free FC is Region-Specific and Subject-Consistent**

Both studies showed topological differences in the multifractal FC. This was more apparent in the $H(2)$ network in the resting-state study, while in the VPR most differences were found in the ΔH_{15} networks. From the two outcomes, the higher variability in the ΔH_{15} networks seems to agree with the fact that multifractality is a more complex property; hence more significant topological differences are to be expected. Even if the resting-state study showed strong intersubject agreement, this was not the case for the VPR study. Two possible explanations are that: *i*) the EEG channels of the VPR study were mainly found in the frontal and parietal cortices, where the greatest subject to subject variability of FC is observed and *ii*) due to the EEG system used in the VPR study, the channels were not always placed in the exact same position for every subject.

- **Scale-free FC Increased in VPR**

The increased $H(2)$ during task shows that temporally-long connections are pruned during rest and reactivated in complex mental tasks. The elevated ΔH_{15} during task could correspond to the increased operation of feedback loops. The current findings agree with previous results from our research lab that showed that FC increases during VPR, using Pearson's correlation. This indicates that the strength of both short-term and long-term connections increases during the task. The difficulty of the tasks did not influence the reorganization of the brain networks, similar to an n-back study that used scale-specific FC estimators.

- **Multifractality Correlates with Reaction Time**

The difference observed in RT and SR within the three difficulty levels suggests that our experimental paradigm effectively stratified the projected images. The positive correlation between $\overline{D^W}$ and RT means that the higher the multifractality of a network, the slower the solving of the VPR task will be. Considering that feedback loops possibly cause/amplify multifractality, this could mean that excessive feedback can be detrimental to the fast solving of a task.

Bibliography of the candidate's publications

Publications related to the thesis:

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