

EEG-BASED FUNCTIONAL BRAIN NETWORKS: HEMISPHERIC DIFFERENCES IN MALES AND FEMALES

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ABSTRACT. Functional connectivity in human brain can be represented as a network using electroencephalography (EEG) signals. Network representation of EEG time series can be an efficient vehicle to understand the underlying mechanisms of brain function. Brain functional networks whose nodes are brain regions and edges correspond to functional links between them are characterized by neurobiologically meaningful graph theory metrics. This study investigates the degree to which graph theory metrics are sex dependent. To this end, EEGs from 24 healthy female subjects and 21 healthy male subjects were recorded in eyes-closed resting state conditions. The connectivity matrices were extracted using correlation analysis and were further binarized to obtain binary functional networks. Global and local efficiency measures as graph theory metrics were computed for the extracted networks. We found that male brains have significantly greater global efficiency (i.e., global communicability of the network) across all frequency bands for a wide range of cost values in both hemispheres. Furthermore, for a range of cost values, female brains showed significantly greater right-hemispheric local efficiency (i.e., local connectivity) than male brains.

1. Introduction. There has been tremendous progress in network science and engineering in recent years [4]. Human brain is one of the most complex biological systems that can be modelled as a networked structure [10]. In modelling the brain as a network, brain regions are considered as nodes and the functional or anatomical relations between them as edges. To construct large-scale functional or anatomical brain networks, signals recorded via electroencephalography (EEG), magnetoencephalography (MEG), or magnetic resonance imaging (MRI) can be used [2, 35, 22]. Brain anatomical networks are extracted using MRI and Diffusion Tensor Imaging (DTI) techniques [19].

It has been shown that real-world networks share a number of common properties such as small-worldness, scale-free degree distribution and community structure [9, 39, 5]. Measuring neurobiologically meaningful graph metrics in brain networks has revealed their small-worldness [2, 15, 33, 34] and scale-free degree distribution [19, 14]. Small-world property of brain networks indicates that the connections have been developed in a way such that the networks have not only rather short average path length (i.e., high global efficiency), but also their transitivity (i.e., clustering coefficient or local connectivity) is rather high (much higher than corresponding random networks). In other words, brain networks are cost economic [11]. Scale-freeness of the networks indicates that there are a small fraction of hub nodes that

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are connected to many nodes (i.e., high degree), while many nodes have only few connections.

Various brain disorders affect the network structure of the brain [8]. It has been shown that the small-world property of brain networks is disrupted in schizophrenia [22, 31], Alzihmers disease [35, 37], epilepsy [28] and patients suffering from psychogenic non-epileptic seizures [6]. The brain networks are also sensitive to the number of nodes considered in the construction process [41, 24]. Therefore, in interpreting properties of brain networks and comparing different works (which might have different sizes for the networks), the size of the networks should be taken into account.

Brains activity is gender-related in some aspects and there are clear anatomical differences between the brain in males and females [25, 17]. Applying DTI technique on a rather large group of subjects revealed their connectivity differences; male brains are optimized for intra-hemispheric and female brains for inter-hemispheric differences [20]. Another DTI study showed that female brains have greater local connectivity than male brains [40]. Furthermore, smaller brains showed larger local connectivity in female brains but in males, and several brain regions were identified to have associations between node centrality and the sex [40]. An fMRI study showed that there are gender-specific interactions in local connectivity of functional brain networks [38].

EEG is a cheap and non-invasive recording technique that is used for both studying mechanisms of brains activity and diagnosis. Gender-specific differences in brains activity are clearly visible in EEGs; the experiments revealed greater bilateral flexibility in females during self-generation tasks [12]. The percentage alpha time was shown to be greater in males, while that of beta time was greater in females [30]. In this work we aimed at studying hemispheric- and gender-specific differences in terms of the global and local connectivity of functional brain networks extracted from EEG time series. First, the weighted connectivity matrices are constructed separately for each hemisphere. Then, global and local efficiency measures are computed for the binarized networks. We observed significant difference between male and female brains. While female brains showed significantly less global efficiency (more pronounced in the left hemisphere) than male brains, females had slightly higher local efficiency than males.

2. Methods.

2.1. EEG recording. The EEGs of 45 healthy subjects, used for this analysis, were recorded at the Department of Clinical Neurosciences of the University of Lausanne (Lausanne, Switzerland) and approved by the local Ethics committee of the university (Commission cantonale d'thique de la recherche sur l'tre humain). All the procedures conformed to the Declaration of Helsinki (1964) by the World Medical Association concerning human experimentation. The participants (21 men with mean age 45 years, standard deviation 16; 24 women with mean age 39 and standard deviation 19) were without substance abuse or dependence and had no known neurological or psychiatric illness or trauma. The participants were all right handed and did not significantly differ in their age ($P > 0.2$; Wilcoxon's ranksum test). Written informed consent was obtained from all participants involved in this study.

The EEG data were collected with eyes closed in a dedicated semi-dark room with a low level of environmental noise. A 128-channel Geodesic Sensor Net (Electrical

Geodesic Inc., Eugene, OR, USA) was used at a sampling frequency of 500 Hz. The sensors from the outer ring of the sensor net were not considered because of low quality signals, which left 111 sensors for analysis. Artifacts in all channels were edited off-line: first automatically, based on an absolute voltage threshold (100 μ V) and on a transition threshold (50 μ V), and then on the basis of a thorough visual inspection. The EEG time series were analyzed in conventional frequency bands including theta (3-7 Hz), alpha (7-13 Hz), beta (13-30 Hz) and gamma (30-50 Hz). To minimize the effects of volume conduction, we computed high-resolution Laplacian [32]. To this end, at each sample, a 2-D spline was fitted to common-average-reference EEG, along the surface of the best-fit sphere.

These control subjects have been previously used in our projects as healthy control signals against patients suffering from schizophrenia, Alzheimers disease and non-epileptic seizures [16, 23, 26].

2.2. Constructing brain functional networks. The filtered EEG time series were used to construct the binary connectivity matrices of the brain networks. The first step to obtain the connectivity matrices is to obtain the weighted correlations. We divided the electrodes into two groups; one for the right hemisphere and another one for the left hemisphere (Fig. 1). We then applied Pearson product momentum correlation coefficient as an index of the interdependence of the time series of two sensor locations. For each hemisphere, we obtained a weighted 51×51 correlation matrix (there are 51 electrodes in each hemisphere) based on Pearson cross-correlation coefficients. The correlation coefficient between sensors i and j can be obtained as

$$r_{ij} = \frac{cov(i, j)}{\sqrt{var(i)var(j)}}, \quad (1)$$

where $cov(i, j)$ is the covariance between nodes i and j , and $var(i)$ is the variance of node i . By averaging the correlation matrices over the artifact-free epochs, we computed two average weighted correlation matrices (one for each hemisphere) for each subject.

The next step was to construct the functional brain networks based on the correlation matrices. A common approach is to binarize the weighted correlation matrices and to compute graph metrics for binary networks. We used conventional application of different threshold values to binarize the correlation matrix and to generate the adjacency matrix [2, 6]. There are different threshold selection methods. When studying group differences, it is important to compare the networks of the same cost. Otherwise, the observed phenomena might be due to the unbalanced number of links in the constructed networks. In order to obtain networks with similar cost, we applied sparsity thresholding method [1, 21, 13]. Cost of an undirected network of size N is the number of its edges divided by the number of edges in a complete network of size N , which is $N(N - 1)/2$. With a cost thresholding method, for each cost value one finds a subject-specific threshold resulting in a network with that particular cost. We applied this procedure to the correlation matrices of all subjects by repeating the thresholding over a range of cost values.

2.3. Graph theoretical metrics. As the binary networks were obtained, we calculated a number of neurobiologically meaningful graph metrics. A number of such measures have been suggested to be meaningful in the context of brain networks [10]. Among them, measures corresponding to global and local connectivity structure of the networks have been frequently used. In this work we studied two such

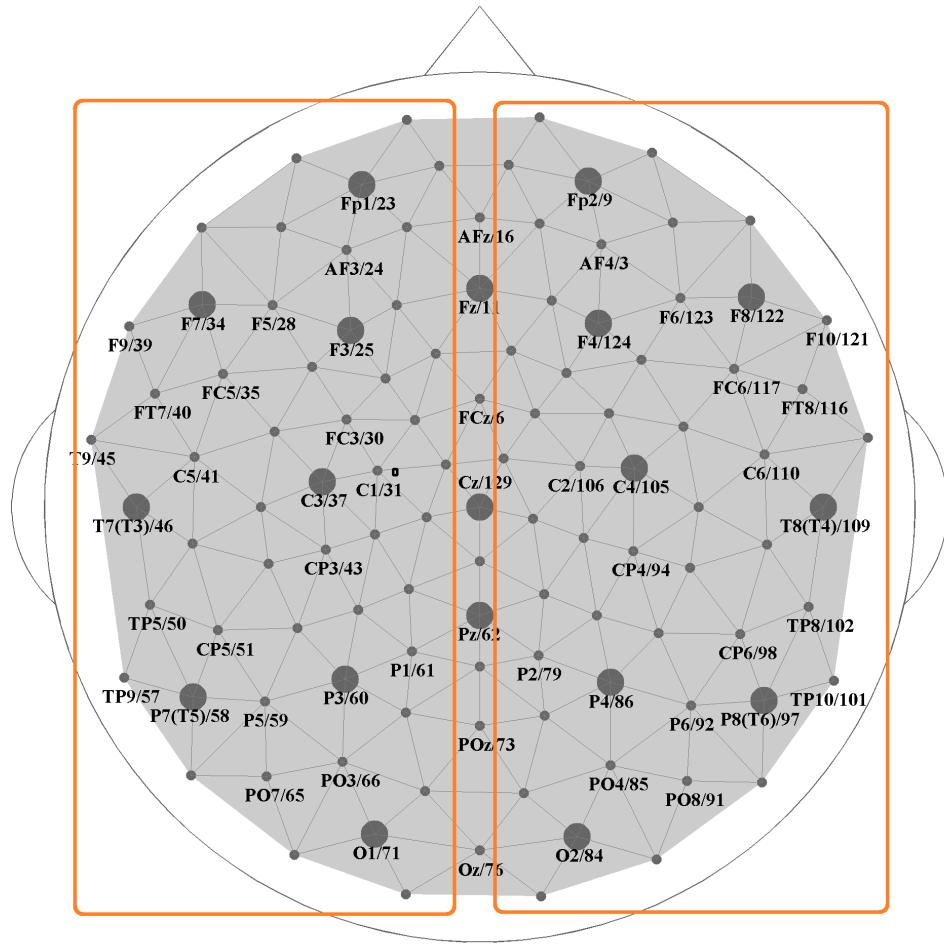


FIGURE 1. The Sensor Net locations that match the positions of the International 10-10 System are labeled and followed by the numbers of the Sensor Net. The sensors corresponding to the 10-20 System are shown with grey circles. The electrodes in the middle are excluded from processing and those inside the rectangular in the right (or left) hemisphere are used to obtain the brain functional networks.

measures: global and local efficiency. Network integration is the ability of a network to combine the information of various parts. A frequently used measure for network integration is global efficiency defined as [27]

$$GE = \frac{1}{N(N-1)} \sum_{i,j} \frac{1}{l_{i,j}}, \quad (2)$$

where N is the total number of nodes in the network and $l_{i,j}$ is the length of the shortest path between nodes i and j .

We also studied local efficiency that determines functional segregation in the brain, which refers to its ability to locally process information in parallel processing

streams. Local efficiency of node i is computed as

$$LE_i = \frac{1}{N_i(N_i - 1)} \sum_{j=G_i} \frac{1}{l_{i,j}}, \quad (3)$$

where N_i is degree of node i (the number of nodes connected to node i) and G_i is the graph of neighbors of nodes i excluding node i . The local efficiency of the network is obtained by making average over all the nodes, more precisely

$$LE = \frac{1}{N} LE_i. \quad (4)$$

2.4. Statistical assessments. Non-parametric Wilcoxon's ranksum test was used to assess the statistically significant differences between the global and local efficiency measures of brain networks at different scales. The tests were carried out separately for all the values of network cost and the difference was considered significant at $P < 0.05$. All the computations were performed in MatLab.

3. Results and discussion. Available tool in network science and engineering have been applied to many real-world systems. These tools have been recently applied for analysing anatomical and functional brain networks constructed based on data recorded from DTI, fMRI, MEG, or EEG. Various brain disorders have been shown to alter their properties. Examples include schizophrenia [22, 31, 3, 7], Alzheimers disease [35, 36], and early blindness [29].

Brain functional networks are often extracted using signals recorded through techniques such as EEG, MEG and fMRI. In these networks, nodes are considered to be brain regions and the links to represent the functional associations between the nodes. In EEG-based functional networks, the nodes are often to be considered the EEG sensor locations [35, 22, 31, 21]. Alternatively, the EEGs in source domain can be used in order to extract the network structure for which the nodes are individual (or a group of) sources. In this work, we analysed properties of EEG-based brain functional networks of a number of male and female subjects. To this end, we extracted networked structure for EEGs recorded from 24 healthy females and 21 healthy males. The EEGs were recorded in eyes-closed resting state, and filtered in conventional frequency bands including theta, alpha, beta and gamma. Furthermore, the networks were studied separately for the hemispheres. Pearson correlation technique was used in order to obtain weighted correlation matrices between the nodes of the networks (i.e., the individual EEG sensor locations in different hemispheres). The weighted correlations were binarized such that the binary networks have the same cost (i.e., the same number of edges). Many graph metrics are sensitive to the number of edges in the networks, and by making the network cost to be the same for all subjects, we removed such unwanted effects.

Figures 2 and 3 show the global efficiency in the left and right hemispheres, respectively. Male brains have significantly greater global efficiency than female brains for a wide range of cost values ($P < 0.05$, Wilcoxon's ranksum test). This is the case for all frequency bands except theta and beta for which there was no significant differences for large cost values. Indeed, when the networks are sparse (for cost values less than 0.2), brain functional networks of male subjects have always significantly greater global efficiency than those of female subjects. The difference in the right hemisphere is less pronounced as compared to the left hemisphere. Global efficiency of right hemisphere in male brain is significantly greater than that of female brain only for a range of medium cost values. Global efficiency corresponds

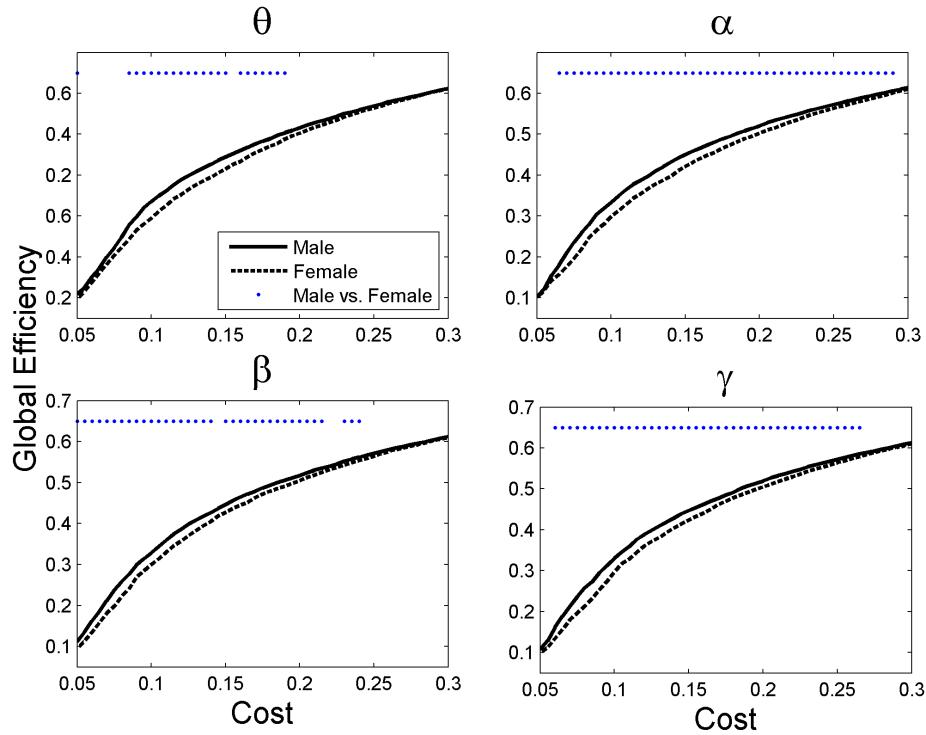


FIGURE 2. Global efficiency of the network as a function of network cost in males and females groups, computed for the left hemisphere. Mean values of clustering coefficient are plotted for different frequency bands including theta (3 - 7 Hz), alpha (7 - 13 Hz), beta (13 - 30 Hz) and gamma (30 - 50 Hz). The dots above the plots represent statistically significant difference at $P < 0.05$ (Wilcoxon's ranksum test).

to communicability of distal brain regions. Our results indicate that male brains have better global communicability than female brains.

Local connectivity of a network is similar to the concept of clustering coefficient (or transitivity) and measures local connectedness of the network. Female brains showed no significant changes in the local connectivity as compared to male brains in the left hemisphere (Fig. 4). However, the right hemispheric local connectivity of functional networks in female subjects showed some significant variations to that of male subjects (Fig. 5). In the right hemisphere, female brains had significantly greater local connectivity than male brains ($P < 0.05$; Wilcoxon's ranksum test) for a range of high cost values in theta and gamma bands, a range of medium to high cost value in alpha band, and a range of medium costs in beta band. These results indicate that the female brains either have greater local connectivity than male brains or there are no significant differences between them.

4. Conclusion. In order to compare the properties of brain functional networks between male and female subjects, we used two frequently used graph metrics: global and local connectivity. Global connectivity of a network is analogous to

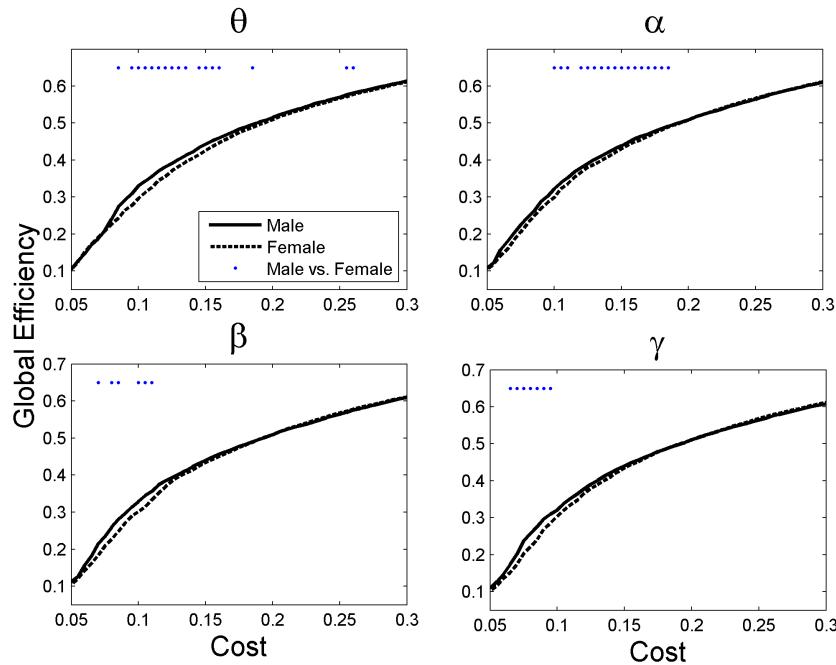


FIGURE 3. Global efficiency of the network as a function of network for the right hemisphere. Other designations are as Fig. 2.

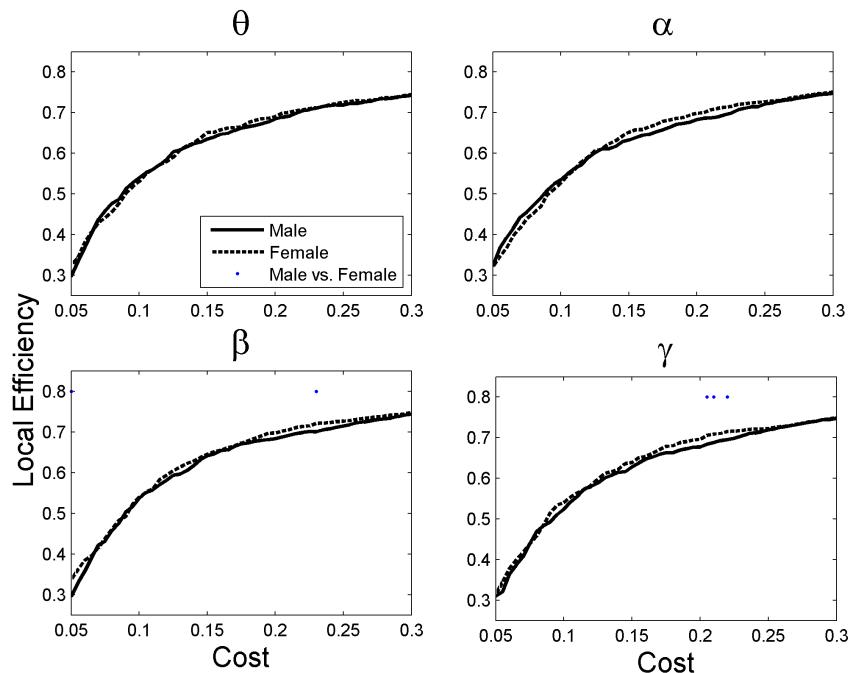


FIGURE 4. Local efficiency of the network as a function of network for the left hemisphere. Other designations are as Fig. 2.

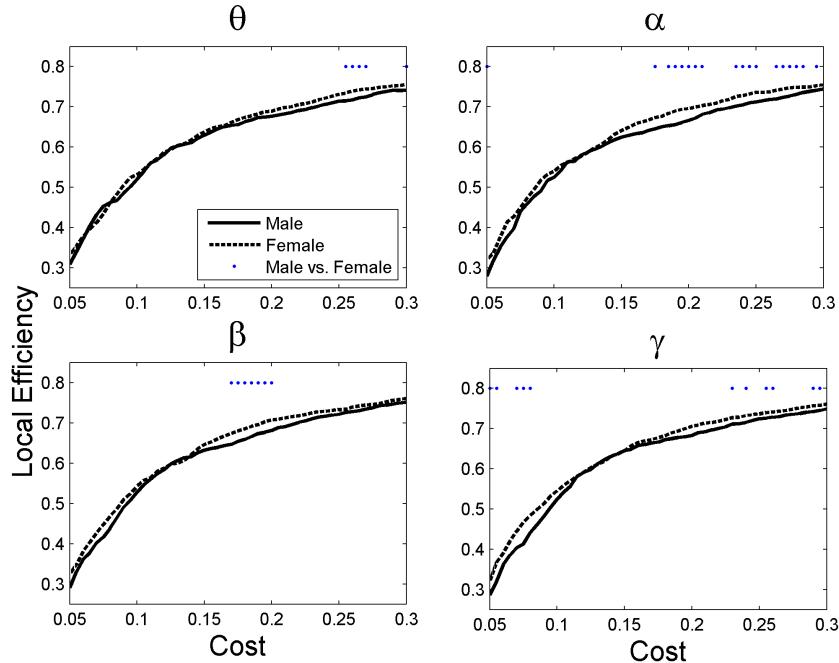


FIGURE 5. Local efficiency of the network as a function of network for the right hemisphere. Other designations are as Fig. 2.

average path length and measure global communicability of the nodes within the networks. The local connectivity is similar to the clustering coefficient and measures local connectedness in the network. We found that male subjects have significantly greater global efficiency than females in the left hemisphere across all frequency bands. Furthermore, males showed greater global efficiency for a range of cost values in the right hemisphere. Contrary to the global efficiency, females showed either no change or greater local efficiency than male subjects. While, we found no significant changes in the local efficiency of the subjects in the left hemisphere, females showed greater local connectivity than males for a range of cost values in functional networks of the right hemisphere.

Our results partially support previous findings on the gender-related differences in cortical connectivity. While, Gong et al showed that female brains have better local/global efficiency in the anatomical connectivity network [18], Tian et al showed that in the functional networks males have higher left-ward local connectivity and lower right-ward local connectivity as compared to female brains [38]. Furthermore, they found no significant differences in the global efficiency measure [38]. Our findings on greater local connectivity for females confirms those based on DTI (i.e., anatomical connectivity), but this is not the case for global connectivity. This work can be replicated on MEG data to investigate whether the MEG-based functional networks depend upon the gender of the subjects.

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REFERENCES

- [1] S. Achard and E. Bullmore, Efficiency and cost of economical brain functional networks, *PLoS Computational Biology*, **3** (2007), e17.
- [2] S. Achard, R. Salvador, B. Whitcher, J. Suckling and E. Bullmore, **A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs**, *The Journal of Neuroscience*, **26** (2006), 63–72.
- [3] A. F. Alexander-Bloch, N. Gogtay, D. Meunier, R. Birn, L. Clasen, F. Lalonde, R. Lenroot, J. Giedd and E. T. Bullmore, Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia, *Frontiers in Systems Neuroscience*, **4** (2010).
- [4] A.-L. Barabási, **Network science**, *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, **371** (2013), 20120375.
- [5] A.-L. Barabási et al., **Scale-free networks: A decade and beyond**, *Science*, **325** (2009), 412–413.
- [6] E. Barzegaran, A. Joudaki, M. Jalili, A. O. Rossetti, R. S. Frackowiak and M. G. Knyazeva, **Properties of functional brain networks correlate with frequency of psychogenic non-epileptic seizures**, *Frontiers in Human Neuroscience*, (2012).
- [7] D. S. Bassett, E. Bullmore, B. A. Verchinski, V. S. Mattay, D. R. Weinberger and A. Meyer-Lindenberg, **Hierarchical organization of human cortical networks in health and schizophrenia**, *The Journal of Neuroscience*, **28** (2008), 9239–9248.
- [8] D. S. Bassett and E. T. Bullmore, **Human brain networks in health and disease**, *Current Opinion in Neurology*, **22** (2009), 340–347.
- [9] S. Boccaletti, V. Latora, Y. Moreno, M. Chavez and D.-U. Hwang, **Complex networks: Structure and dynamics**, *Physics Reports*, **424** (2006), 175–308.
- [10] E. Bullmore and O. Sporns, **Complex brain networks: Graph theoretical analysis of structural and functional systems**, *Nature Reviews Neuroscience*, **10** (2009), 186–198.
- [11] E. Bullmore and O. Sporns, **The economy of brain network organization**, *Nature Reviews Neuroscience*, **13** (2012), 336–349.
- [12] R. J. Davidson, G. E. Schwartz, E. Pugash and E. Bromfield, **Sex differences in patterns of eeg asymmetry**, *Biological Psychology*, **4** (1976), 119–137.
- [13] F. De Vico Fallani, L. Astolfi, F. Cincotti, D. Mattia, D. la Rocca, E. Maksuti, S. Salinari, F. Babiloni, B. Vegso and G. Kozmann, et al., Evaluation of the brain network organization from eeg signals: A preliminary evidence in stroke patient, *The Anatomical Record*, **292** (2009), 2023–2031.
- [14] V. M. Eguiluz, D. R. Chialvo, G. A. Cecchi, M. Baliki and A. V. Apkarian, **Scale-free brain functional networks**, *Physical Review Letters*, **94** (2005), 018102.
- [15] R. Ferri, F. Rundo, O. Bruni, M. G. Terzano and C. J. Stam, **Small-world network organization of functional connectivity of eeg slow-wave activity during sleep**, *Clinical Neurophysiology*, **118** (2007), 449–456.
- [16] E. Fornari, P. Maeder, R. Meuli, J. Ghika and M. G. Knyazeva, **Demyelination of superficial white matter in early Alzheimer's disease: A magnetization transfer imaging study**, *Neurobiology of Aging*, **33** (2012), 428.e7–428.e19.
- [17] G. Gong, Y. He and A. C. Evans, **Brain connectivity gender makes a difference**, *The Neuroscientist*, **17** (2011), 575–591.
- [18] G. Gong, P. Rosa-Neto, F. Carbonell, Z. J. Chen, Y. He and A. C. Evans, **Age-and gender-related differences in the cortical anatomical network**, *The Journal of Neuroscience*, **29** (2009), 15684–15693.
- [19] P. Hagmann, L. Cammoun, X. Gigandet, R. Meuli, C. J. Honey, V. J. Wedeen and O. Sporns, **Mapping the structural core of human cerebral cortex**, *PLoS Biology*, **6** (2008), e159.
- [20] M. Ingalhalikar, A. Smith, D. Parker, T. D. Satterthwaite, M. A. Elliott, K. Ruparel, H. Hakonarson, R. E. Gur, R. C. Gur and R. Verma, **Sex differences in the structural connectome of the human brain**, *Proceedings of the National Academy of Sciences*, **111** (2014), 823–828.
- [21] M. Jalili and M. G. Knyazeva, **Constructing brain functional networks from eeg: Partial and unpartial correlations**, *Journal of Integrative Neuroscience*, **10** (2011), 213–232.
- [22] M. Jalili and M. G. Knyazeva, **Eeg-based functional networks in schizophrenia**, *Computers in Biology and Medicine*, **41** (2011), 1178–1186.

- [23] M. Jalili, S. Lavoie, P. Deppen, R. Meuli, K. Q. Do, M. Cuénod, M. Hasler, O. De Feo and M. G. Knyazeva, **Dysconnection topography in schizophrenia revealed with state-space analysis of eeg**, *PLoS One*, **2** (2007), e1059.
- [24] A. Joudaki, N. Salehi, M. Jalili and M. G. Knyazeva, **Eeg-based functional brain networks: Does the network size matter?**, *PloS One*, **7** (2012), e35673.
- [25] D. Kimura, Sex differences in the brain, *Scientific American*, **267** (1992), 118–125.
- [26] M. G. Knyazeva, M. Jalili, R. S. Frackowiak and A. O. Rossetti, **Psychogenic seizures and frontal disconnection: Eeg synchronisation study**, *Journal of Neurology, Neurosurgery & Psychiatry*, **82** (2011), 505–511.
- [27] V. Latora and M. Marchiori, **Economic small-world behavior in weighted networks**, *The European Physical Journal B-Condensed Matter and Complex Systems*, **32** (2003), 249–263.
- [28] W. Liao, Z. Zhang, Z. Pan, D. Mantini, J. Ding, X. Duan, C. Luo, G. Lu and H. Chen, **Altered functional connectivity and small-world in mesial temporal lobe epilepsy**, *PloS One*, **5** (2010), e8525.
- [29] Y. Liu, C. Yu, M. Liang, J. Li, L. Tian, Y. Zhou, W. Qin, K. Li and T. Jiang, **Whole brain functional connectivity in the early blind**, *Brain*, **130** (2007), 2085–2096.
- [30] M. Matsuura, K. Yamamoto, H. Fukuzawa, Y. Okubo, H. Uesugi, M. Moriwa, T. Kojima and Y. Shimazono, **Age development and sex differences of various eeg elements in healthy children and adults-quantification by a computerized wave form recognition method**, *Electroencephalography and Clinical Neurophysiology*, **60** (1985), 394–406.
- [31] S. Micheloyannis, E. Pachou, C. J. Stam, M. Breakspear, P. Bitsios, M. Vourkas, S. Erimaki and M. Zervakis, **Small-world networks and disturbed functional connectivity in schizophrenia**, *Schizophrenia Research*, **87** (2006), 60–66.
- [32] P. L. Nunez and R. Srinivasan, **Electric Fields of the Brain: The Neurophysics of EEG**, 2nd edition, Oxford university press, 2006.
- [33] O. Sporns, **Small-world connectivity, motif composition, and complexity of fractal neuronal connections**, *Biosystems*, **85** (2006), 55–64.
- [34] O. Sporns and J. D. Zwi, **The small world of the cerebral cortex**, *Neuroinformatics*, **2** (2004), 145–162.
- [35] C. Stam, W. De Haan, A. Daffertshofer, B. Jones, I. Manshanden, A. V. C. Van Walsum, T. Montez, J. Verbunt, J. De Munck and B. Van Dijk, et al., **Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer’s disease**, *Brain*, **132** (2009), 213–224.
- [36] C. Stam, B. Jones, G. Nolte, M. Breakspear and P. Scheltens, **Small-world networks and functional connectivity in Alzheimer’s disease**, *Cerebral Cortex*, **17** (2007), 92–99.
- [37] M. S. Tahaei, M. Jalili and M. G. Knyazeva, **Synchronizability of eeg-based functional networks in early alzheimer’s disease**, *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, **20** (2012), 636–641.
- [38] L. Tian, J. Wang, C. Yan and Y. He, **Hemisphere-and gender-related differences in small-world brain networks: A resting-state functional mri study**, *Neuroimage*, **54** (2011), 191–202.
- [39] D. J. Watts and S. H. Strogatz, **Collective dynamics of ‘small-world’ networks**, *Nature*, **393** (1998), 440–442.
- [40] C. Yan, G. Gong, J. Wang, D. Wang, D. Liu, C. Zhu, Z. J. Chen, A. Evans, Y. Zang and Y. He, **Sex-and brain size-related small-world structural cortical networks in young adults: A dti tractography study**, *Cerebral cortex*, **21** (2011), 449–458.
- [41] A. Zalesky, A. Fornito, I. H. Harding, L. Cocchi, M. Yücel, C. Pantelis and E. T. Bullmore, **Whole-brain anatomical networks: Does the choice of nodes matter?**, *Neuroimage*, **50** (2010), 970–983.

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