FUNCTIONAL COLLECTIVITY OF COMPLEX BRAIN NETWORKS

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Summary

Brain function is carried out by an astronomically large network of interconnected

neurons. Thanks to the impressive progress in brain imaging techniques an increasing amount of spatiotemporal brain data is now available. The analysis of this data using statistical physics approaches allows for a reduction of the brain spatiotemporal dynamics into information flow on a complex network. Using this view, recent studies revealed that these brain networks share several principles with natural, social and technological systems. These notes summarize the most relevant advances in our understanding of the brain using this approach.

1. Introduction - The Brain is A Network

Brain function is carried out by a network of approximately 10^{10} interconnected neurons. An increasing amount of spatiotemporal brain data is now available thanks to the impressive progress in brain imaging techniques in particular with functional Magnetic Resonance Imaging (fMRI). To analyze such a large and complex body of information, conceptual approaches grounded in statistical physics have been used recently. This work showed that the dynamics of these patterns can be reduced to complex networks that share several principles with natural, social and technological systems. The aim of these notes is to describe the most relevant advances in our understanding of the brain using this approach, focusing only on those results providing clues about the underlying critical dynamics of the brain. Other excellent surveys providing a broader perspective, including medical applications can be found in Sporns et al (2004), Bassett and Bullmore (2006), Reijneveld et al (2007), Bullmore and Sporns, (2009).

The chapter is organized as follows. After introducing the problem, section 2 describes how brain networks are derived. Section 3 describes the initial brain imaging experiments showing a broad distribution of functional connectivity, implying that brain networks are scale-free. Section 4 discusses how these scale-free properties are conceptually linked to critical dynamics in physical systems. This includes a detailed comparison between the brain results with those extracted from a paradigmatic critical system; the Ising model. Section 5 is dedicated to discuss the implications and the final section summarizes the conclusions.

2. Extracting Brain Functional Networks from the Data

Brain activity evolves continuously over a network of gargantuan size and complexity, therefore and it is crucial before attempting any meaningful analysis to reduce the data to a manageable size. One possible focus is on the *interactions* between brain sites, and uses that information to construct the adjacency matrix defining a network, often called “correlation network”. This is something done previously in many other systems as for instance, to study the interactions between cell proteins (Jeong et al, 2001) or gene expression (Stuart et al, 2003). In this manner, the problem is reduced to the study of a graph composed by nodes (sites) and links (interactions). The cartoon in Figure 1 illustrates these steps after the brain data is collected, as described by Eguiluz and colleagues (Eguiluz et al, 2005). Each snapshot of brain activity in this type of experiments is a fMRI image composite from the so-called BOLD (blood oxygenated level dependent) signal, which is a directly related to the level of neuronal activity in any given brain site. Typically the spatial resolution is of about 36 slices (3 mm thick) from top to bottom of the brain, divided equally into a 64 by 64 matrix (3.475 mm x 3.475 mm wide) resulting in approximately cubic regions called voxels. The activity is recorded at consecutive intervals (in this case every 2.5 sec.) to produce typically 400 samples. As was stated above, the interest is to use the interactions between brain sizes to define a network. For simplicity, this is done computing the correlation between sites within a time window. Denoting the activity in voxel x at time t as $V(x,t)$ then the linear correlation coefficient between all pair of voxels, x_i and x_j is computed as:

$$r(x_i, x_j) = \frac{\langle V(x_i,t) \quad V(x_j,t)\rangle - \langle V(x_i,t)\rangle\langle V(x_j,t)\rangle}{\sigma(V(x_i))\,\sigma(V(x_j))} \qquad (1)$$

where $\sigma^2(V(x)) = \langle V(x,t)^2\rangle - \langle V(x,t)\rangle^2$ and the quantities inside brackets represent temporal averages.

In principle, as it is discussed later, networks can be built by defining negative or positive correlations, although the initial results were obtained using positive correlations. Thus, pairs of voxels whose correlation r exceeds a threshold ρ are considered functionally linked. Of course, if one chooses a threshold too small, then the majority of the voxels will appear to be connected to one another. Likewise if the threshold is too high, then voxels will appear isolated. There is a wide range of threshold values for which networks remain clearly defined indicating that the main conclusions are robust with respect to the selection of parameters.

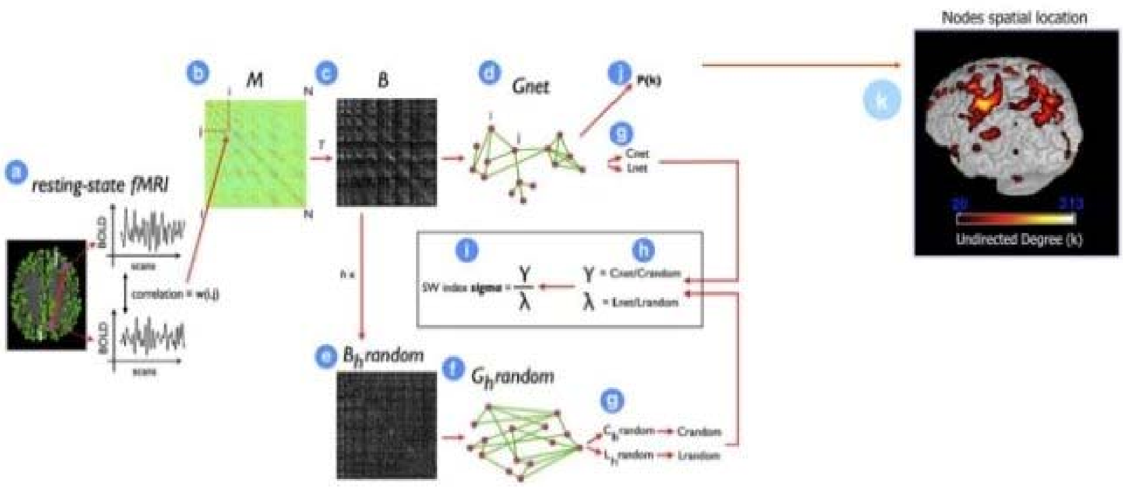

Figure 1. Steps to derive the networks from the BOLD fMRI signals. The correlation between fMRI signals (a) is computed to obtain a correlation matrix (b). The elements in the matrix passing a given threshold (c) define the network (d). Randomizing the nodes location, (e) a random network is obtained (f) and used to compare several statistics (g-j) with the original network. The node spatial location (k) can be also visualized.

3. Brain Correlation Networks Are Scale Free

An example of a brain network extracted using this method is shown in Figure 2. For clarity, only one eighth of the nodes are included in this illustration. The pattern of inhomogeneous connectivity is immediately evident by the fact that a relatively large proportion of nodes have a single link and a smaller proportion of nodes exhibit numerous connections. A quantitative estimate of this inverse relationship is shown in the bottom panel of Figure 2 demonstrating a skewed distribution of the number of links with a tail approaching a distribution $p(k) \sim k^{-\gamma}$ $p(k) \sim k^{-\gamma}$ (with γ around 2). This power law is more evident for networks constructed with higher thresholds; i.e., less correlated conditions. For networks constructed with lower thresholds, a maximum appears which shifts to the right as ρ decreases.

The small inset in panel B of Figure 2 shows the distribution of links of a surrogate network constructed by randomly shuffling the original time sequence of each voxel´s magnetic resonance signal. This is done to reject the possibility that the network arises from correlations non related to brain dynamics. The degree distribution of these surrogate networks does not fit a power law, but rather display a Gaussian distribution in which the mean and width depend on the ρ threshold used. These results reported by Eguiluz and colleagues demonstrate that brain dynamics, at this relatively large scale, evolves over a scale free network. These initial finding are now confirmed by other authors (Van der Heuvel et al, 2008) in a variety of experimental settings indicating that a few brain regions are very well connected (the right of the distribution), many more regions are only interacting with a few others, and a broad intermediate situation can be found to exist between these two extremes.

Other calculations revealed that the average number of links as a function of -physical-distance between brain sites also decays as a power law, implying that there is no characteristic length for the interactions between any two brain sites (Eguiluz et al 2005). Two other statistical properties of these networks, path length and clustering were computed as well (Boccaletti et al 2006). The path length (L) between two voxels is the minimum number of links necessary to connect both voxels. Clustering (C) is the fraction of connections between the topological neighbors of a voxel with respect to the maximum possible.

Measurements of L and C were also made in a randomized version of the brain network. The main finding was that L remained relatively constant in both cases while C in the random case resulted much smaller, implying that brain networks are "small world" nets, a property with several implications in terms of cortical connectivity. Further calculations revealed that the distribution of links amongst neighbors are positively correlated, in other words, highly connected nodes connect with highly connected ones and vice versa.

This was a surprising finding since this property, known as assortativity, is mostly found in social networks but not seen previously in biological systems, were the rule is that negative correlations regulate connectivity. Summarizing, the initial work of Eguiluz et al. showed that functional brain networks exhibit highly inhomogeneous scale-free functional connectivity with small world and assortativity properties.

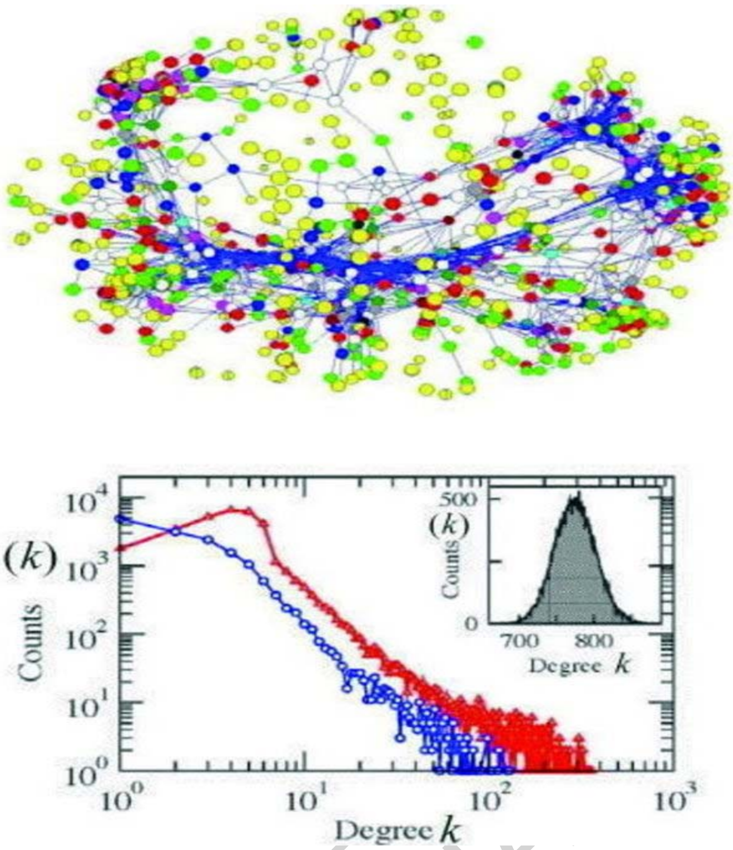

Figure 2. A typical brain network extracted from functional magnetic resonance imaging. Top panel shows a pictorial representation of the network where the nodes are colored according to its degree: yellow=1, green=2, red=3,blue=4, etc. The bottom panel shows the degree distributions for networks constructed with two correlation thresholds: $\rho = 0.7$ (blue circles) and $\rho = 0.6$ (red triangles). The inset depicts the degree distribution for an equivalent randomly connected network.

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Bibliography

Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. (2006). Resilient, low frequency, small-world human brain functional network with highly connected association cortical hubs. *Journal of Neuroscience*, 26, 63–72. [Human brain functional networks are derived from frequency-dependent correlation matrices between 90 cortical and subcortical regions and shown to possess small-world properties with highly connected cortical hubs].

Albert R, Barabasi AL. (2002). Statistical Mechanics of Complex Networks, *Rev. Mod. Phys*. 74, 47. [A review emphasizing the ubiquity of scale free networks]

Bak P. (1997). *How nature works*. Oxford, UK: Oxford University Press. [A masterpiece presenting in a very provoking manner that, in all the instances natural phenomena can be associated and understood as critical phenomena].

Bak P, Chialvo D R. (2001). Adaptive learning by extremal dynamics and negative feedback. *Physical Review E*, 63, 031912. [A provoking paper dedicated to question mainstream ideas about brain learning and to demonstrate how simple could be the process on a network guided by extremal dynamics. Includes the initial arguments for the role of criticality in the brain].

Baliki MN, Geha PY, Apkarian AV, Chialvo DR. (2008). Beyond feeling: chronic pain hurts the brain disrupting the default-mode network dynamics. *Journal of Neuroscience* 28(6) 1398–1403. [A fMRI study showing the chronic effects of pain over brain dynamics].

Balleza E, Alvarez-Buylla E, Chaos A, Kauffman S A, Shmulevich I, Aldana M. (2008). Critical dynamics in genetic regulatory networks: examples from four Kingdoms, *PLoS ONE*, 3, 2456. [Numerical evidence of critical dynamics underlying the regulation on four types of genetic networks, see also Nykter et al, 2008].

Bassett DS, Bullmore E. (2006). Small-world brain networks. *Neuroscientist*, 12, 512–523. [A recent review on brain networks, emphasizing results obtained form networks derived by a small number of predefined anatomical regions].

Beckers R, Deneubourg J-L, Goss S, Pasteels JM. (1990). Collective decision making through food recruitment. *Insectes Sociaux*, 37, 258–267. [Earlier papers on collectives swarm effects].

Beekman M, Sumpter DJT, Ratnieks FLW. (2001). Phase transition between disordered and ordered foraging in Pharaoh's ants. *Proc. Natl. Acad. Sci. USA* 98, 9703–9706. [An account of phase transition in ants dynamics].

Beu M, Baudrexel S, Hautzel H, Antke Chr, Mueller H-W. (2009). Neural traffic as voxel-based measure of cerebral functional connectivity in fMRI. *Journal of Neuroscience Methods* 176, 263–269. [The authors rename the approach used in Eguiluz et al 2005, as "neural traffic" (NT) and provide evidence for its validity showing that this approach reveals a more extended neural network when compared to measures correlating regional brain activity with the time course of an external stimulus].

Bienenstock E, Lehmann D, (1998). Regulated Criticality in the Brain? *Advances in Complex Systems*, 1, 361-384. [One of the first workable neural models having a critical point as an attractor].

Boccaletti S, Latora V, Moreno Y, Chavez M, D.-U. Hwang. (2006). Complex networks: Structure and dynamics, *Physics Reports* 424 (175 – 308 . [A recent multidisciplinary review of work on complex networks]

Buchanan M. (2000). *Ubiquity*. London, UK, Weidenfeld and Nicolson. [The ubiquity of power laws in nature is presented at a level amenable to general audience].

Bullmore E, Sporns O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci.* 10(4):312. [A review presenting the evolution of the topic, see also the preceding one by Sporns et al, 2004].

Caldarelli G. (2007). *Scale-Free Networks complex webs in nature and technology*, Oxford University Press. [A recent book on scale-free networks]

Chialvo DR, Millonas M M (1995). How swarms build cognitive maps. In L. Steels (Ed.) *The biology and technology of intelligent autonomous agents.* NATO ASI series 144, 439–450. [Together with Rauch et al 2005, this paper describe the first mathematical model of the collective dynamics of moving agents on a changing field].

Chialvo DR, Bak P. (1999). Learning from mistakes. *Neuroscience* 90, 1137-1148 [A provoking paper dedicated to question mainstream ideas and to demonstrate how simple could be learning if it is guided by mistakes. Includes the initial arguments for the role of criticality in the brain].

Chialvo DR. (2004). Critical brain networks. *Physica A* 340, 756-765. [An account of the efforts towards identifying instances of criticality in the brain, a paper dedicated to the late Per Bak].

Chialvo DR (2006). Are our senses critical? *Nature Physics* 2, 301-302. [A commentary on the advantages of criticality on brain networks, see also the motivating article by Kinouchi and Copelli, 2006].

Chialvo DR. The brain near the edge. In J. Marro, P. L. Garrido, & J. J. Torres (Eds.) (2007).*Cooperative behavior in neural systems: Ninth Granada Lectures*. AIP Conference Proceedings 887, 1–12. [Essay discussing the conjecture that the brain is near a critical point].

Chialvo DR. (2008), Emergent complexity: What uphill analysis or downhill invention cannot do. *New Ideas in Psychology* 26, 158-173. [Essay dedicated to discuss the conjecture that the brain is near a critical point].

Eguiluz VM, Chialvo DR, Cecchi GA, Baliki M., Apkarian AV. (2005). Scale-free brain functional networks. *Phys. Rev. Lett.,* 94, 018102. [The first results deriving functional networks from measurements in the human brain and characterizing their statistical properties].

Fraiman D, Balenzuela P, Foss J, Chialvo DR (2009). Ising-like dynamics in large-scale brain functional networks. *Phys. Rev. E,* 79, 061922. [Shows evidence that brain dynamics could be critical. Comparing networks from human brain fMRI data and from simulations of the Ising model at the critical temperature this work shows that they are undistinguishable from each other].

Fukuda K, Takayasu H, Takayasu M. (2000). Origin of critical behavior in Ethernet traffic. *Physica A* 287, 289–301. [Evidence for criticality in Ethernet traffic].

Jeong H, S.P. Mason, A.-L. Barabási, Z.N. Oltvai (2001). Lethality and centrality in protein networks. *Nature* 411, 41. [Provide support to the idea that the phenotypic consequence of a single gene deletion depend on the topological position of its protein product in the complex web of molecular interactions].

Kelso JAS, Bressler SL, Buchanan S, DeGuzman GC, Ding M, et al. (1992). A phase transition in human brain and behavior. *Phys Lett A* 169:134–144. [Evidence that during a changing bimanual coordination task the dynamics of the brain changes phase]

Kinouchi O, Copelli M, Optimal dynamical range of excitable networks at criticality. Nature Physics, 2, 348–352. (2006). [It shows that networks models at the critical point exhibit the widest dynamical range].

Linkenkaer-Hansen K, Nikouline VV, Palva JM, Ilmoniemi RJ (2001). Long-range temporal correlations and scaling behavior in human brain oscillations. *J. Neurosci* 21, 1370. [Experiments showing the presence of power law correlation in slow frequency brain oscillations].

Lux T, Marchesi M (1999). Scaling and criticality in a stochastic multi-agent model of a financial market. *Nature*, 397:498–500. [Numerical evidence from a multi-agent model that the market might be critical].

Malamud BD, Morein G, Turcotte DL (1998). Forest fires: An example of self-organized critical behavior. *Science*, 281, 1840–1842. [Statistical analysis of forest fires data indicating that they may belong to critical dynamics].

Metropolis N, Rosenbluth A W, Rosenbluth M N, Teller A H, Teller E. (1953). Equations of State Calculations by Fast Computing Machines. *Journal of Chemical Physics* 21, 1087-1092. [The description of the numerical method for the Montercalo simulations].

Newman M.E.J. (2003). The structure and function of complex networks, *SIAM Review,* 45, 167-256. [This review focus on the mathematical modeling of networks, including random graph models and their generalizations].

Newman M.E.J. (2002). Assortative mixing in networks, *Phys. Rev. Lett*. 89, 208701. [Presents measures of assortativity and examples for real networks].

Nicolis G, Prigogine I (1977). *Self-Organization in Non-equilibrium Systems: From Dissipative Structures to Order Through Fluctuations* (Wiley, New York).[A classical textbook on Non-equilibrium Systems]

Nykter M, Price ND, Aldana M, Ramsey SA, Kauffman SA, Hood LE, Yli-Harja O & Shmulevich I. (2008). Gene expression dynamics in the macrophage exhibit criticality. *Proc. Natl. Acad. Sci. USA*. 105(6):1897-1900. [A numerical experiment showing that gene expression may be near a critical point, see also Balleza et al 2008].

Paczuski M, Bak P. (1999). Self-organization of complex systems. In Proceedings of 12th Chris Engelbrecht Summer School. Eprint arxiv.org cond-mat/9906077. [A excellent review of the connection between complexity and criticality].

Peters O. and Neelin D. (2006). Critical phenomena in atmospheric precipitation. *Nature Phys.* 2, 393-396 [A demonstration that rain, at very large scale, corresponds to critical dynamics]

Rauch E M, Chialvo DR, Millonas M M. (1995). Pattern formation and functionality in swarm models. *Physics Letters A*, 207, 185–193. [The first realistic mathematical model of agents moving on an evolving field exhibiting self-organized collective effects of the kind seen in nature].

Reijneveld J C, Ponten S C, Berendse H W, Stam C J. (2007). The application of graph theoretical analysis to complex networks in the brain. *Clinical Neurophysiology,* 118, 2317-2331. [A extensive review of work in networks in neuroscience].

Salvador R, Suckling J, Coleman M R, Pickard J D, Menon D, Bullmore E. (2005). Neurophysiological architecture of functional magnetic resonance images of human brain. *Cerebral Cortex*, 15, 1332–1342. [Human brain functional networks are derived from correlation matrices between ninety cortical and subcortical regions. Its shows that the network exhibits small-world properties and lack scale invariant degree distribution].

Sporns O, Chialvo DR, Kaiser M, Hilgetag C C. (2004). Organization, development and function of complex brain networks. *Trends in Cognitive Sciences*, 8,418–425. [A review presenting the initial results on the topic, see also a more recent account by Bullmore and Sporns, 2009].

Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens, Ph (2007). Small-world networks and functional connectivity in Alzheimer's disease. *Cerebral Cortex,* 17, 92–99. [Describes alterations of brain networks properties in disease]

Stam CJ, (2004). Functional connectivity patterns of human magnetoencephalographic recordings: a "small-word" network? *Neuroscience Letters*, 355, 25-28. [Networks derived from the matrix of synchronization strengths between 128 sites of the magnetoencephalograms obtained in healthy human subjects].

Stuart J M, Segal E, Koller D, Kim S K, (2003), A gene-coexpression network for global discovery of conserved genetic modules. *Science,* 302 (5643) 249 - 255. [Study of gene functional networks defined from pairs of genes that are coexpressed in DNA microarrays from humans, flies, worms, and yeast].

Takayasu M, Takayasu H, Fukuda K (2000). Dynamic phase transition observed in the Internet traffic flow. *Physica A,* 277, 248–255. [A paper on the dynamical properties of the exchange of information in Internet]

Turcotte D L. (1999). Self-organized criticality. *Reports on Progress in Physics,* 62, 1377–1429. [An extensive review of work related to the topic of self-organized criticality].

Turing A, (1950). Computing machinery and intelligence. Mind, 59, 433-460. E. A. Feigenbaum and J. Feldman (eds.), *Computers and thought.* New York: McGraw-Hill. [The classical Turing discussion about machines and intelligence].

Van der Heuvel M. P et al, (2008). Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain, *Neuroimage,* 43, 528 [Confirmed and extended Eguiluz et al. 2005 findings in brain functional networks, including the power law scaling of the degree].

Watts, D. J. *Small Worlds: The dynamics of networks between order and randomness* (Princeton Univ. Press, Princeton 1999). [An account of the small world topic, amenable to general readership].

Werner G. (2008). Dynamics across levels of organization. *Journal of Physiology – Paris.* 101, 273-279. [An authoritative perspective about recent and potential contributions of statistical physics to brain science].

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