

An informational approach to the Network Disease Hypothesis in resting state fMRI

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Abstract Here we combine graph and information theory based approaches to understand network robustness in resting state-fMRI (R-fMRI). We calculate how the network robustness is affected upon the removal of nodes in the functional connectivity network in resting state for elder subjects compared to young subjects. We provide a measure of network robustness and we show that this measure can be used as a predictor of aging. We argue that the discovery of network based biomarkers for neurodegenerative conditions will rely on the combination of both graph theoretic and informational approaches in R-fMRI.

Key words: resting state fMRI, network degeneration hypothesis, Markov chain, relative entropy

1 Introduction

The objective of this work is to study robustness i.e., resilience to perturbations, in resting state functional connectivity networks. It has been suggested that fluctuations in the BOLD signal measured in humans in resting state, represent the neuronal activity baseline and shape spatially consistent patterns [1], [2]. These slow fluctuations in the BOLD signal found in resting subjects, are highly coherent within either structural or functional networks in the human brain. Therefore, exploring these fluctuations could lead to a better understanding of the brain's intrinsic or spontaneous neural activity. Functional correlation based on the synchrony of low-frequency blood flow fluctuations in resting state, have been identified in the sensorimotor [3], visual [4], language [5], auditory [6], dorsal and ventral attention

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[7] and the frontoparietal control system [8]. The systematic study of those patterns using correlation analysis techniques has identified a number of resting state networks, which are functionally relevant networks found in subjects in the absence of either goal directed-task or external stimuli.

The visual identification of the overall connectivity patterns in resting state functional magnetic resonance imaging (R-fMRI), has been assessed using either model-based and model-free approaches. In the former, statistical parametric maps of brain activation are built upon voxel-wise analysis location [9]. While this approach has been successful in the identification of motor networks, it shows important limitations when the seed voxel cannot be easily identified [10]. For example, in brain areas with unclear boundaries i.e., cognitive networks involved for instance, in memory or self processing operations [11]. Independent Component Analysis (ICA), on the other hand, is a model-free approach that allows separating resting fluctuations from other signal variations, resulting on a collection of spatial maps, one for each independent component, that represent functionally relevant networks in the brain [12]. While ICA has the advantage over model-free methods that it does not need to assume a specific temporal model of correlation between regions of interest, the functional relevance of the different components is, however, computed relative to their resemblance to a number of networks based on criteria that are not easily formalized [13]. Graph-based techniques have proliferated in the last years providing new insights into the structure function relationship in the healthy brain, and in aging and neuropathological disorders [?], [14], [15]. Prove of the utility of this approach is that notable proponents of a modularist vision of brain connectivity to understand cognition, such as Gazzaniga [16] (see [17] for an early critic of the modularist approach by Fuster who anticipates a shift toward networks) has now embraced the complex brain networks approach to understand the interplay between structure and function in brain systems [18].

Network-based approaches to R-fMRI data have demonstrated non-trivial topological properties of functional networks in the human brain. Among these is the knowledge that the brain's intrinsic activity is organized as a small-world, highly efficient network, with significant modularity and highly connected hub regions. These network properties have also been found to change throughout normal development, aging, and in various pathological conditions. Graph theory provides a theoretical framework to investigate the overall architecture of the brain. Specifically, the topological organization of brain networks has been recently studied with graph theory. The use of graph theoretic techniques to model brain networks has shifted the emphasis from the identification of local subnetworks -default mode network, primary sensory motor network etc.- to the quantitative study of the topological and informational characteristics of large-scale brain networks.

The application of graph theoretic analysis has demonstrated non-trivial topological properties of functional networks in the human brain. Large-scale anatomical connectivity analysis in the mammalian brain, shows that brain topology is neither random nor regular. Instead, small world architectures [19] -highly clustered nodes connected thorough relatively short paths- have been identified in brain networks. Small world networks are not solely structural, functional networks with a small

world organization have been identified in the mammal brain [20]. These network properties have also been consistently found across different conditions, including normal development, aging, and in various pathological conditions. For a review of network analysis in resting-state functional MRI, see [14].

Computational simulations of disruptions in the network architecture of resting state can give clues about normal development and pathological conditions. For example, Supekar and colleagues [21] have shown that the deterioration of small world properties such as the lowering of the cluster coefficient, affect local network connectivity, which in turn may work as a network biomarker for Alzheimer’s disease. Abnormalities in small-worldness may also have a significant positive correlation in, for example, schizophrenia [22] and epilepsy [23]. While network-based studies have been successful in delineating generic network properties, such as path length or clustering, additional work is needed in order to come to grips with the internal working of the systems underlying the network. In this paper we investigate the effects of aging in resting state functional connectivity networks using a methodology that combines graph and information theoretic tools. We systematically study how network robustness -functional network invariance under perturbation- is affected upon the removal of nodes in the functional connectivity network in resting state for both young and elder subjects.

The rest of paper is structured as follows. In section 2 the methodology followed in the data acquisition and reconstruction, data preprocessing, and data connectivity analysis in two conditions -23 young and 19 elder individuals- is presented. Then, we build a model to study quantitatively how network robustness is affected upon the removal of nodes in the functional connectivity network in both conditions. We provide a ranking of nodes that quantifies the impact of their obliteration using a network efficiency measure based on [24] that quantifies how the network efficiency in transmitting information deteriorates once a node is removed from the network. The empirical and clinical implications of the theoretical model here are described in the results section 3. The paper concludes with a discussion section 4.

2 Materials and Methods

2.1 Data acquisition

Forty-two healthy volunteers separated in two groups, young (ages 21-32; mean 22.7) and elder (ages 51-59) took part in the fMRI experiment. All subjects had normal or corrected-to-normal vision. The study was approved by the ethics committee of Okayama University, and written informed consent was obtained before the study. All subjects were imaged using a 1.5 T Philips scanner vision whole-body MRI system (Okayama University Hospital, Okayama, Japan), which was equipped with a head coil. Functional MR images were acquired during rest when subjects were instructed to keep their eyes closed and not to think of anything in particu-

lar. The imaging area consisted of 32 functional gradient-echo planar imaging (EPI) axial slices (voxel size=3x3x4 mm³, TR=3000 ms, TE=50 ms, FA=90°, 64x64 matrix) that were used to obtain T2*-weighted fMRI images in the axial plane. We obtained 176 functional volumes and excluded the first 4 scans from analysis. Before the EPI scan, a T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence was acquired (TR=2300 ms, TE=2.98 ms, TI=900 ms, voxel size=1x1x1 mm³).

2.2 Data preprocessing

Data were preprocessed using Statistical Parametric Mapping software SPM8¹ and REST v1.7². To correct for differences in slice acquisition time, all images were synchronized to the middle slice. Subsequently, images were spatially realigned to the first volume due to head motion. None of the subjects had head movements exceeding 2.5 mm on any axis or rotations greater than 2.5°. After the correction, the imaging data were normalized to the Montreal Neurological Institute (MNI) EPI template supplied with SPM8 (resampled to 2x2x2 mm³ voxels)³. In order to avoid artificially introducing local spatial correlation, the normalized images were not smoothed. Finally, the resulting data were temporally band-pass filtered (0.01-0.08 Hz) to reduce the effects of low-frequency drifts and high-frequency physiological noises [?].

2.3 Anatomical parcellation

Before whole brain parcellation, several sources of spurious variance including the estimated head motion parameters, the global brain signal and the average time series in the cerebrospinal fluid and white matter regions were removed from the data through linear regression. Then, the fMRI data were parcellated into 90 regions using an automated anatomical labeling template [25]. For each subject, the mean time series of each region was obtained by simply averaging the time series of all voxels within that region.

¹ <http://www.fil.ion.ucl.ac.uk/spm/>

² <http://restfmri.net/forum/index.php>

³ <http://imaging.mrc-cbu.cam.ac.uk/imaging/Templates>

2.4 Brain network construction

To measure the functional connectivity among regions, we calculated the Pearson correlation coefficients between any possible pair of regional time series, and then obtained a temporal correlation matrix (90x90) for each subject. We applied Fisher's r-to-z transformation to improve the normality of the correlation matrix. Then, two-tailed one-sample t-tests were performed for all the possible 4005 i.e., $\frac{90 \times 89}{2}$ pairwise correlations across subjects to examine whether each inter-regional correlation significantly differed from zero.

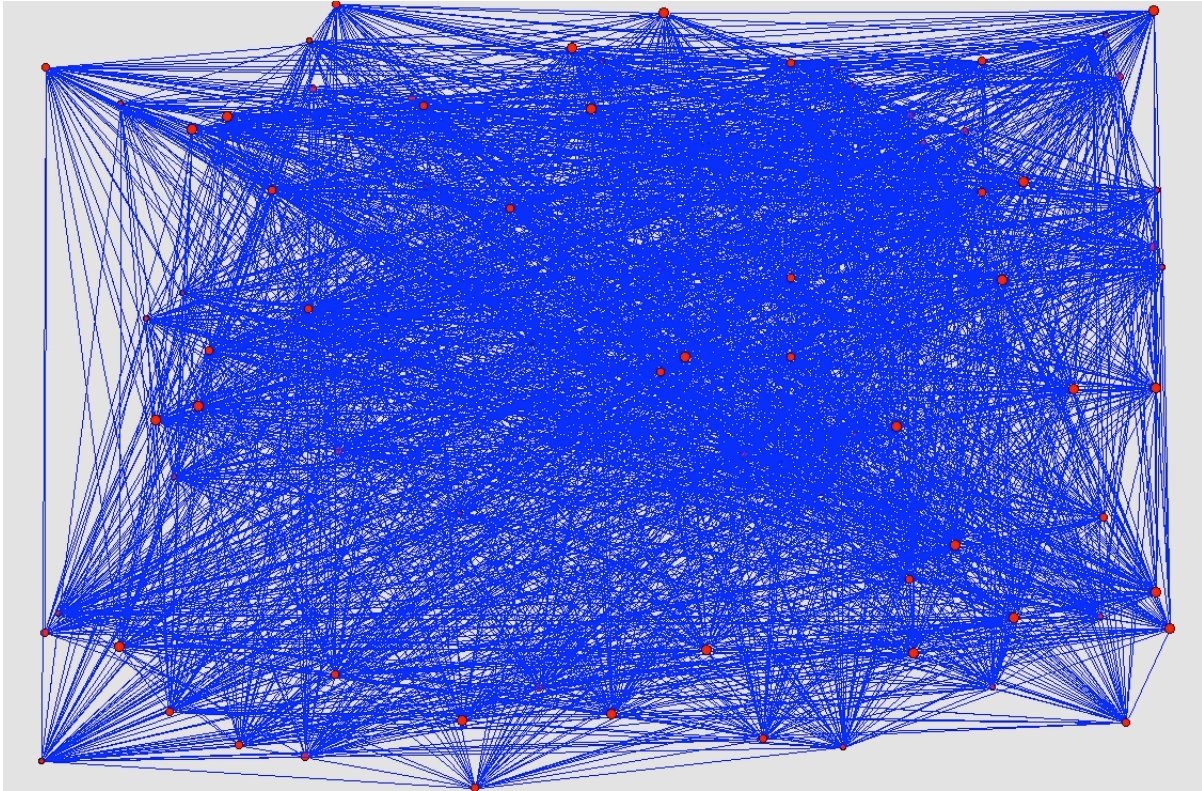


Fig. 1 Graphic representation of the functional connectivity among regions based on the temporal correlation matrix of the twenty-three healthy controls, using Pajek software [?]

A Bonferroni-corrected significance level of $P < 0.001$ was further used to threshold the correlation matrix into an adjacency matrix whose element was 1 if there was significant correlation between the two brain regions and 0 otherwise. Finally, an undirected binary graph was acquired in which nodes represent brain

regions and edges represent links between regions. The study of the connectivity distribution of the resulting adjacency matrix is provided in the Appendix ??.

2.5 Network-based model on robustness

A quantitative understanding of network robustness, that is, functional network invariance under perturbation can shed light on the properties that mediate in developmental, aging and pathological processes in the human brain. In essence, robustness measures the capacity of the network to perform the same function before and after a perturbation. Perturbations are events, internal or external, that elicit a change in the network configuration, as for example in, to obliterate a node or a change in the connectivity between nodes. Thus, for a given network $G(N, E)$ a perturbation δ (e.g., the removal of a set of nodes M from N) transforms the initial graph $G(N, E)$ into $G(N - M, E - E(M))$, where $N - M$ is the remaining set of nodes after having deleted the set M and $E - E(M)$ is the set of edges that do not connect any of the deleted nodes in M . The robustness of the new network $G(N - M, E - E(M))$ resulting of the perturbation δ can be studied as a loss in the network efficiency Σ driven by the elimination of a set of nodes M and the edges that connect them. The efficiency of a network G , $\Sigma(G)$, is a network centrality measure that quantifies the network's reliability in transmitting information once a node or a set of nodes have being removed. One possible measure of network efficiency can be calculated using the Latora and Marchiori measure [24]. Accordingly, the efficiency in the communication between any two nodes in a graph G is equal to the inverse of the shortest path that connects them or

$$\varepsilon_{ij} = \frac{1}{d_{ij}} \quad (1)$$

The efficiency of the graph is calculated as the average of the efficiency between any two nodes ε_{ij}

$$\Sigma(G) = \frac{\sum_{i \neq j \in G} \varepsilon_{ij}}{N(N-1)} = \frac{1}{N(N-1)} \frac{1}{\sum_{i \neq j \in G} d_{ij}} \quad (2)$$

where N is the number of nodes and d_{ij} is the shortest path length (the geodesic distance) between nodes i and j . Note that when there is no path that connects the nodes i and j , $d_{ij} = \infty$, and the efficiency in the communication of the two nodes is zero, $\varepsilon_{ij} = 0$.

Finally, the robustness measure, \mathcal{R} , is defined as the relative performance retained or efficiency loss under a network insult i.e., a perturbation δ , that transforms the initial network G into G^δ .

$$\mathcal{R}^\delta = \frac{\Sigma(G^\delta)}{\Sigma(G)} \quad (3)$$

Thus, from equation 3, a network G is considered to be robust to a perturbation δ if the network efficiency $\Sigma(G)$ stays close to the original value after a perturbation, ideally $\mathcal{R}^\delta = \frac{\Sigma(G^\delta)}{\Sigma(G)} = 1$.

We can, in addition to robustness and efficiency of any given graph G , calculate the information centrality C of any node i in the network G as the variation in the network efficiency caused by the removal of the edges incident in i . The centrality of a node i , C_i , is calculated as the difference between the efficiency of the original graph G with N nodes and E edges, $G(N, E)$, and the efficiency of the resulting graph G_i with N nodes and $E - k_i$ edges, where k_i denotes the set of edges incident to node i . Thus, the centrality of a node is a normalized measure of the loss in network efficiency caused by the isolation of a node in G .

$$C_i = \frac{\Sigma(G(N, E)) - \Sigma(G(N, E - k_i))}{\Sigma(G(N, E))} \quad (4)$$

By the same token, the information centrality of a set of nodes S can be calculated as normalized measure of the loss in network efficiency caused by the isolation of a set of nodes S in G .

$$C_S = \frac{\Sigma(G(N, E)) - \Sigma(G(N, E - k_S))}{\Sigma(G(N, E))} \quad (5)$$

3 Results

The global network efficiency is 0.3678 for young subjects and 0.1144 for elder subjects. Thus, young subjects connectivity network is three times more efficient in terms of the shortest path distance between any two nodes.

In Table ?? (see Excel file) is shown the information centrality for each of the AAL regions.

We have analyzed the functional connectivity in resting state of both young and elder individuals. The nodes representing the ninety brain regions based on the AAL parcelation have been ranked in terms of their impact in terms of network robustness upon removal. Interestingly we find that in both elder and young groups the removal of certain nodes does not necessarily triggers a decrease in network robustness, the obliteration of certain nodes may also produces a positive impact in the network function, increasing the network robustness when the node is removed. We study network robustness based on the new network efficiency/performance measure (equation 2) to investigate the network functionality when a set of nodes are obliterated. The results show that in young subjects, the nodes with a positive impact are ... TO DO LI/JAIME compared with elder subjects ... TO DO LI/JAIME.

In the second part we use information-theoretic measures to study the impact of the removal of nodes in the network. First, we model the network flows in terms of a stationary Markov chain which describes how a particle walks randomly from node

to node, in both the young and elder functional connectivity graph. The probability transition matrix is derived from the binary adjacency matrix using the local property of connectivity degree. The entropy rate of a random walk on a graph in which a node or group of nodes has been removed is calculated.

The results show that in young subjects, after the removal of the nodes with a positive impact the entropy rate is $> < ?$ TO DO JAIME than in the case of elder subjects.

4 Discussion

The literature reviewed here suggests that graph-based network analyses are capable of uncovering system-level changes associated with different processes in the resting brain, which could provide novel insights into the understanding of the underlying physiological mechanisms of brain function. We also highlight several potential research topics in the future. Graph theory-based approaches model the brain as a complex network in which nodes represent brain regions of interest and the edges connecting nodes represent relationship between nodes e.g., functional connectivity. Researchers using graph-theory based methods have been able to not only visualize brain networks, but to quantify their topological properties. Graph theory provides a geometric representation to visualize brain connectivity patterns and an analytic toolbox to quantitatively characterize the overall topological organization. A new theoretical framework to investigate network robustness and how it is affected by internally driven processes such as aging is provided.

We provide a quantitative measure of network robustness upon the removal of nodes and its edges in a tvity network (RS) and then to compare these results with a network dynamics approach which goes beyond ranking of n a network snapshot to try to infer which are the crucial nodes to keep the network properly working.

5 Appendix

Information is a concept too broad to be captured in a single definition, however, for any probability distribution we have the entropy, which is a quantity that agrees with the intuitive notion we may have about information. Entropy can be extended to the mutual information which is the amount of entropy that one random variable contains about another. Entropy is then a special case of the MI because, entropy is the self information of a random variable, $H(X)=MI(X,X)$. And MI is a special case of the relative entropy or distance between two probability distributions.

H is special case of MI is a special case of relativeH or KL

Notation: The entropy of a random variable, $H(X)$ but we can also write $H(p)$ where p is the pmf of the r.v. X . Note that $p(x)=Pr(X=x)$, for all x in the support of X .

A stochastic process is a indexed sequence of random variables and it can be described as the joint probability mass function. A stoch process is stationary if the joint distribution is invariant with time shifts. A distribution on the states at time n = Markov is an example of a stoch. process with dependence, each r.v depends respoecc to shifts in the time index. on the one preceding it and is conditionayy independent of all the other preceding r.v. [?]

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