Understanding network adaptation in Resting-State fMRI: a information theoretic approach

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Network theory approaches to brain connectivity in Resting-State fMRI have been mainly focused on the study of topological properties and network motifs that characterize the network structure. Small world architectures -highly clustered nodes connected thorough relatively short paths- have been identified in healthy and functional brain networks. It has been suggested that the disruption of normal brain function in diseases such as Schizophrenia and Alzheimer's disease, can be observed and measured in terms of variations in the network topology. For example, the reshaping of small-worldness into randomness in functional connectivity networks. This posits new venues to the study of brain disease prognosis in terms of network-based biomarkers. However, a formal understanding of the interplay between brain disease and network connectivity is still missing. Here we build a information based theory of robustness, in which rather than quantify how global graph properties -efficiency, global cost etc.- are modified upon node removal, we study how network connectedness is altered by biased random walks, that is random walks that follow a given strategy, for example, favor the visit of nodes with high betweenness centrality. Thus, each strategy -a vector containing nodes weights- produces a new network in response of an insult. We calculate then the Kullback-Leibier distance between these networks that represent different adaptive strategies and the pre-disturbance network. A new approach for network robustness in Resting-State fMRI and how it compares to traditional vulnerability-based studies is provided.

brain function | bias | decision making | subjective value | utility function

Introduction

The method that study BOLD fluctuations that spontaneously emerge during awake rest is called resting state fMRI (R-fMRI), and the networks that are identified with such a methodology are resting state networks (RSNs). Resting state networks have been identified in a panoply of imaging techniques including fMRI [3], PET [30] (first identification of the Default Mode Network), near-infrared spectroscopy (NIRS) [32], EEG [27], [5] and fMRI combined with diffusion-based studies -diffusion tensor imaging (DTI) [38] and high angular resolution diffusion imaging (HARDI) [26]. Data analysis of resting state data falls into two gropus: seed-based and model-free methods. In the former, a functional connectivity map of regions of interest or seeds is obtained. The map represents the correlation between the resting-state time-series of the different seeds, which have been a priori selected [10], [16], [7], [4]. Model-free methods also provide a connectivity map across brain regions, but here the regions of interest are obtained through statistical analysis, rather than defined a priori as in the mode-based approach. A number of model-free computational tools exist to analyse resting-state time series, including independent component analysis [2] , [13], , clustering [35], [37] and machine learning techniques such as support vector machines [25], [43]. For a critique on the use of the "minimal assumption" adopted in model-free approaches such as ICA in neuroimage data analysis, see [**?**].

Seed-based methods are relatively straight forward to use and conteptually simple. A disadventage is that the functional connectivity map here obtained is strictely dependent on the regions of interest previosly selected, overlooking the rest of brain areas and therefore falling to notice potentially relevant functional connection patterns. Model-free methods, on the other hand, explore functional connectivity at whole-brain scale. Independent component analysis allows direct comparison between subject groups [9], but presents the disadventage that it provides a number of different networks (components) whose biological relevance and consistency with previous findings need to be validated by other means. Note that model-based approaches avoid this dificulty by adopting the seeds or regions of interest a priori, either by selecting the relevant regions from a separate fMRI in a task experiment, or using a brain atlas in rest activity studies [40], [14].

Clustering and machine learning methods e.g., SVM, allow individual-based classification analysis. This is an important advantage to traditional group analyses of variance, and may bring important insights into disease onset prediction on individual subject basis [41]. Importantly, the above described approaches taken together show consistency in their results, that is, the functional maps tend to overlap across resting-state studies in the human brain [**?**].

It is important to realize that resting state networks are not the same as intrinsic connectivity networks (ICNs), which refer to network or components identified through multivariate decomposition statistical analysis e.g., independent component analysis (ICA), that show synchronous fluctuations during task performance. Therefore, RSNs are a sub class of ICNs which comprehend a set of large-scale functionally connected brain networks not only in resting state but also in task-based neuroimaging data.

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 [29], [17]. Functional correlation based on the synchrony of low-frequency blood flow fluctuations in resting state, have been identified in the sensorimotor [22], visual [12], language [18], auditory [19], dorsal and ventral attention [15] and the frontoparietal control system [39].

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 patters 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.

Reserved for Publication Footnotes

This approach has been successful in the identification of motor networks, but it shows important limitations when the seed voxel cannot be easily identified. For example, in brain areas with unclear boundaries; i.e. cognitive networks involved for instance, in language or memory. 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. While ICA has the advantage over model-free methods that it is unbiased, (that is, it does not need to posit a specific temporal model of correlation between ROIs), 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. More recently, researchers using graph-theory based methods have been able to not only visualize brain networks, but to quantify their topological properties. Large-scale anatomical connectivity analysis in the mammalian brain, shows that brain topology is neither random nor regular. Instead, it is organized in small world architectures [42], [36], characterized by high clustering and short path lengths. Small world networks are not solely structural, functional networks with a small world organization have been identified in the mammal brain [1]. In addition to this, disruptions in the small world organization can give clues about normal development and pathological conditions. For example, Supekar and colleagues [34] 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 [24] and epilepsy [23] (Y. Li More refs here). 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. Robustness in brain connectivity has been typically approached in terms of the impact that the complete disruption and/or removal of a network component has in the network topology [21]. However, by focusing on the topology of the network, factors that may play a key role in the network's vulnerability to failures can be neglected. For example, it has been suggested that patients with Alzheimer's disease show an increment in brain activity in certain areas relative to healthy subjects that compensates for the disease related atrophy of other regions [31]. In this paper we explore the network degeneration hypothesis [33], [28], which states that neurological diseases target functional neural networks modifying its topological properties, using a methodology that combining graph theoretic tools and information theory may rigorously address robustness and its interplay in aging and pathological conditions. This approach posits a new theoretical framework to investigate network robustness and how it is affected by "internal perturbations" such as aging and neurological disorders.

Despite the variability in the data acquisition protocols, statistical data analysis and gropus of subjects employed by different researchers, the litterature consistenly shows an overlap of functionally linked networks in the brain during resting state. The most commonly reported resting state networks are at least eight: the primary sensorimotor network, the primary visual and extra-striate visual network, bilateral temporal/insular and anterior cingulate cortex regions, left and right lateralized networks consisting of superior parietal and superior frontal regions, and the default mode network [**?**].

Graph Theory:a brain-scale approach. Until the recent advent of graph theoretic methods in RS-fMRI, the focus was put on the identification of anatomically separated regions that show a high level of functional correlation during rest. Grapth theory provides a theoretical framework to investigate the overall architecture of the brain. Thus, the emphasis has shifted from the identification of local subnetworks -default mode network, primary sensory motor network etc.- to the assesment of the topological and informational characteristics of a brain-scale complex network. The tools we use to model a system may also convey an ontological version of it, that is to say, the system under study is seen through the lens of a specific approach that necessarly shapes the observability domain. Thus, the identification of different subnetworks during rest can be seen as a by-product of the techniques used, for example identification component analysis (ICA) or clustering. On the other hand, the emphasis on the overall brain functional architecture might not suprised when using graph theoretic methods. Notable proponents of a modularist vision of brain connectivity to understand cognition -[**?**], [20]- have shifted toward a network-based approach- [**?**].

Clinical applications of RS-fMRI. Functional connnectivity studies of neurological and neuropsychitatric disorders are being copiously produced. Resting-state functional magnetic resonance imaging experiments are considerably less demanding in terms of subject oparticipation than performace studies.This is of the outmost importance in dealing with subjects (patients) with their cognitive or motor capabilities reduced due pathological conditions. Altered resting-state functional connectivity patterns have been shown in an impressive range of pathologies and conditions - Alzheimer's disease, schizophrenia, multiple sclerosis, Parkinson's disease, depression, autism, and even attention deficit/ hyperactivity disorder. See [**?**] for a review on clinical applications of rs-fMRI at the single subject level.

RS- fMRI have been successfully used in classification of subjects with AD and MCI versus healthy controls. Connectivity changes in the default mode network can be used as markers of pathological conditions. For example, patients with tivity in the salience network. Alzheimer disease demonstrated decreased connectivity in the default mode network but increased connectivity in the salience network. Other studies rather than focusing on specific RSNs -default mode network- investigate altered connectivity patterns at a brain-wide level. The hypothesis that neurological disorders target large-scale functional and structural networks [33] rather than specific loci or sub-networks, calls for an integrative network-based approach.

Schizophrenia patients show a decreased functional connectivity during rest [**?**] suggesting a suboptimal information integration between regions of the brain network [**?**] AD patients show clustering coefficients significantly lower in patients compared with controls.

Network Degeneration Hypothesis in ICN(state of the art). R-fMRI studies avoids the problem of task-evoked BOLD fluctuations and is easier to implement in subjects with their cognitive or motor capabilities reduced as in Alzheimer's or Parkinsons's disease.

The network degeneration hypothesis -disease starts in small network assemblies, to progressively spread to connected areas of the initial locus- has been investigated in a number of brain pathologies including Alzheimer's disease [6], epilepsy [23], schizophrenia [24] and unipolar depression [25]. The NDH encompasses the idea that neurodegeneration can be studied as a network dysfunction process, in which changes in the network organization are informative about the progression of the disease. This paves the way for a network-based approach to diagnosis of neural disorders, and the discovery of network biomarkers in early disease detection. To our knowledge, the first attempt to systematically test the NDH is in [33], in which Seeley and colleagues use functional and structural network mapping approaches to characterize five distinct neurodegenerative syndromes. There is a growing body of evidence that neurodegenerative disease targets specific large-scale brain networks, and clinical applications

However, it might be emphasized that the empirical validation of the network degeneration hypothesis does not tell us much about the mechanisms that mediate in the alleged network connectivity sensitivity to neuropathological syndromes. A critical aspect is to understand network robustness, that is, functional network invariance under perturbation. In essence, robustness measures the capacity of the network to perform the same function before and after a perturbation. Perturba-

tions 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 $G(V, E)$ with an adjacency matrix T, a perturbation d_A that transforms T into a new adjacency matrix T_A is given by the stochastic map $d_A : T \rightarrow T_A$. Here, we assume that the perturbation d_A refers to the set of nodes that remained after having deleted the set of nodes $V - A$. Therefore, originally the network $G(V, E)$ is transformed into $G(A, E^A)$, where E^A are the remaining edge that results of eliminate the nodes $V - A$ from V. Contrary to standard robustness studies reviewed in section **??** that measure the effect of network insults -typically node removal- in terms of macroscopic properties such as cost, efficiency or entropy, here we focus on the different adaptive processes that may follow the network disruption, and we are able to identify the strategies that promote function invariance. The Kullback-Leibler distance allows to answer the question of which of a set of approximating models is closest to the original model f. This is a classical problem of model selection in which the Kullback-Leibler distance allows elucidate which model in a set of candidate models, $g(x|\theta)$, is the closest to the true model $f(x)$. Accordingly, the best candidate is that with minimum distance. Thus, the minimum distance between f and g in the case of discrete distributions is given by:

$$KL(f, g) = \sum_{i=1}^{n} p_i \log(\frac{p_i}{q_i}) \qquad [1]$$

where n is the number of possible outcomes of the underlying random variable, p_i is the probability distribution of the ith outcome and q_i is the approximating probability distribution. The KL distance is not a true metric since is not symmetric, as the distance is different from the distance. For a more in detailed description of KL, see [11]

It is important to note that KL cannot be computed unless we have a full knowledge of both the true model f and the parameters θ in g_θ. While this requirement is often unrealistic for observational studies, specially in biology, it holds in the present case [8]. The applicability of this approach relies upon the fact that "true model" f is given by the network adjacency matrix T prior to the insult d_A and the parameters θ in g_θ can be assigned to a vector $b_i = b_{i1}, \ldots, b_{i|A|}$ that assigns specific weights to each node in T_A, the resulting adjacency matrix of the perturbation d_A readjusted with a bias or strategy b_i, in which the passage through certain nodes are favored related to others. For example, a bias or adaptive strategy in which random walkers are more likely to visit nodes with highest betweenness centrality can be constructed straight forward by increasing the weight of the edges that lead to those nodes.

Network Robustness. network topology that promotes Functional invariance Figure

Model selection. which probability distribution

Methods

Results

Discussion

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