School of Informatics

Informatics Research Review
Analysis of Functional Connectome in human brain

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Abstract

Recent developments in computational neuroscience have brought us a step closer to understanding the human brain. The review concentrates on analyzing functional connectome (dynamic representation of the correlation between parts of the brain) at an individual level to get insights into the internal working of the brain when engaged in various ways. The review also focuses on understanding the "fingerprinting"(identify uniquely) ability of the functional connectome and the parameters that affect it.

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1 Introduction

Computational Neuroscience is an interdisciplinary field between neuroscience, cognitive science, mathematics, and computer science[1]. The ultimate aim of this newly emerging field is to explain how information is represented and processed in our brain and the underlying mechanisms that perform them. Recent developments in the past decade and the increased use of artificial intelligence have unlocked new potential in this field. Until 2013, most of the research in the field was concentrated on group-level studies to draw inferences about the human brain and generalize it. With the introduction of the Human Connectome Project [2], the interest in the field shifted towards personalized studies to unravel the hidden aspects of the working of the brain at an individual level. These studies have paved a path to understanding certain brain-related diseases [3].

It is a well-established fact that the human brain has highly developed cognitive functions. One of the open research questions in the field is how this cognitive ability changed with evolution[4]. Some of the well-known adaptations that our brain went through include enlargement of cortical areas, changes in genetics, etc.[5]. These adaptations have changed the brain connectome which refers to the comprehensive map of the neural connections in the brain that form a network. The analysis of such networks are studied at various scales, from the level of neurons to the level of brain regions/networks.

At the microscopic level, the connections between neurons are formed by exchanging chemical signals called synapses. Whereas at the macroscopic level, communication is done through neural pathways that connect various regions of the brain. These regions (voxels) are used as biomarkers and can be defined using various parcellation techniques. The two main modes of connectivity in the brain are structural connectome and functional connectome. This paper concentrates on the functional connectome also defined as the functional network in the brain that often changes depending on the state and actions performed by the brain. In this review group related inferences are not included but concentrates more on individual level inferences.

This review paper discusses about functional connectome and the ability to uniquely identify it. Some of the questions discussed in this paper include:

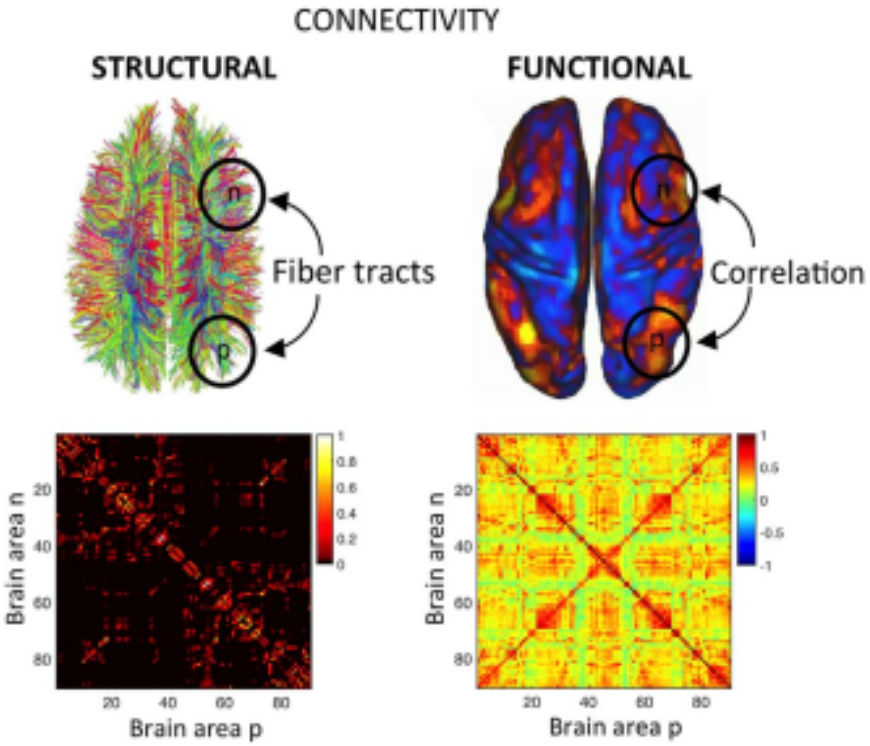
1. Is the functional connectome unique at an individual level and what are the underlying principles that are responsible for it?
2. What effects does cognitive processes have when analyzing functional connectome?
3. How parcellation schemes effect the functional connectome analysis?
4. What role does time and age play in this analysis and supporting research in such scenarios?

Since it is a rising field most of the research material covered is from past decade with some exceptions of old research that forms basis for some of the discussed literature. Most of the discussed material are from peer reviewed journals, articles where the journals had an impact factor in range of 3-6. It is to be noted that all the general and basic information required to understand the literature review part of the paper are provided in section **1.1**. The literature review concentrates on critical analysis of the material. In section **3** common practises exercised in all the experiments are mentioned along with their importance.

1.1 Background

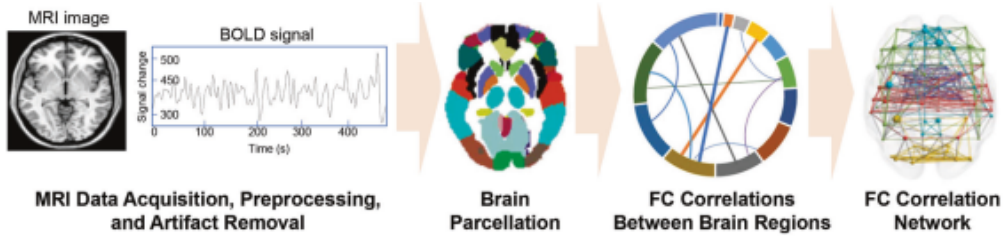
Structural connectome(SC) is defined as the network formed by white matter fibers that connect different areas of the brain [6]. It can also be defined as a wiring diagram of the brain. At the microscopic level, the neurons try to communicate with each other by passing chemical signals using action potentials. Since we cannot have fully mapped the anatomical connections in the brain due to a huge number of connections in the range of 100 trillion connections between 100 billion neurons. So for feasible analysis of the brain, we study at the macroscopic level where the interesting regions of the brain are defined as nodes, and the anatomical connection is referred to as the structural network of the brain. The structural variations tend to change very slowly with time due to aging or diseases [7]. So it is acceptable that the structural network is static by nature.

Functional Connectome(FC) is generally referred to as the whole map of functional connections across the whole brain[8]. There is no direct method to observe the communication between these networks but we can do so indirectly by analyzing the flow of blood in the regions. It is observed that when there was a spike due to neural activity there was blood flow in that region this signal is called the Blood Oxygen Level Dependent(BOLD) Signal [8]. It showed a high correlation with neural activity and is hence used as an indirect measure to observe signals between regions of the brain network over time(FC). These signals are easily obtained using the fMRI imaging process. The image shown below explains difference between structural and functional connectome i.e structural connectome is the anatomical connections between regions and the matrix in the image shows physical link between two regions in the brain. Functional connectome is the dynamic network formed on SC and the matrix represents correlation between the regions of the brain.



To obtain the functional connectivity network over the whole brain we collect the BOLD signal

from each interesting region of the brain the process that defines the interesting regions of the brain is called parcellation techniques. Due to the recent use of Machine learning algorithms, there are new parcellation techniques defined which improved the understanding of regions of the brain that communicate with each other and their underlying topology [9]. After defining the parcellation technique and taking the BOLD signal from those regions of interest we calculate the correlation matrix between these defined nodes for some period this is called the functional connectivity correlation matrix and it can be easily understood using the below image.



Workflow diagram of FC [10]

2 Literature Review

This review concentrates on a few base research papers([11], [12], [13],[14]) followed by some supporting research papers. The authors conducted various experiments with different human subjects to better understand how the functional network of the brain works for different cognitive tasks. This part of the section discusses comparisons based on some important aspects. For every new paper that is introduced the following sequence of questions were answered :

1. What are the research questions the authors tried to answer regarding the functional connectome of the brain?
2. What kind of dataset was used along with the details of the type of imaging scans performed?
3. What brain parcellation technique was used to construct the functional connectome matrix?
4. Then key findings were critically reviewed based on the available literature.

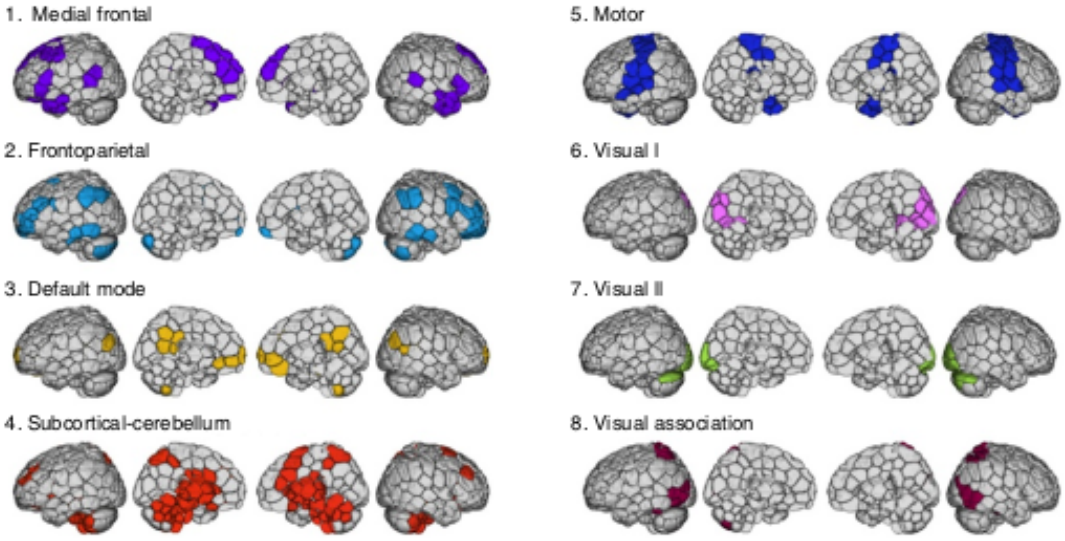
It is to be noted that the papers which were introduced, do not follow strict chronological order instead they are grouped according to sections which help in improved comparison.

2.1 Functional Connectome "fingerprinting"

The authors of the paper [11] wanted to understand the functional networks on an individual level while performing basic cognitive tasks. They used the data from the Q2 data release of the Human Connectome Project (HCP)[15] which consists of Functional Magnetic Resonance Imaging (fMRI) scans from 126 subjects(40Males,86Females) where each subject was scanned over 2 days. The experiments performed included data from 6 different(cognitive tasks) imaging conditions two rest sessions and four task sessions(emotion, motor, language, memory), on each day a rest session was followed by 2 task sessions where each session lasted for few minutes.

The authors set up 268 nodes as parcellation scheme at different parts of brain according to groupwise parcellation scheme defined by [16] which is a common parcellation scheme used. They used the data from 268 nodes and created a correlation matrix of size 268 X 268 to see whether the correlation between the interesting regions of the brain remained the same for rest, task states (whole-brain level study).To compare the similarity between the matrices pearson correlation was used as a metric . They could identify 117/126 people(92.9%) based on the rest state matrices taken from two different days. Similarly, when it was tested using the task state matrices obtained on two days they found out the accuracy was in a range of 87% for a task to task comparisons. Since the authors think that the 126 trials were not independent they performed a non-parametric permutation test to find the significance of their results and found out that the highest accuracy they achieved was 5% for 1000 iterations proving that the results obtained were not by chance.

To see whether some underlying networks contribute to the accuracy levels they used spectral clustering algorithm [16] to further classify nodes into networks. They found ten such networks exist and used eight specific networks to test their hypothesis. It was found that two networks contributed more to individual subject identification medial frontal network, frontoparietal network. Now they run the same algorithm which was used at the whole-brain level and found that when both networks were used a higher classification rate of 98-99% is achieved for rest state matrices which outperform the whole-brain level accuracy along with the individual network performance. For the task state, it was around 80-90%. This proved that certain regions of the brain contribute more to the inter-individual classification.



To see how the parcellation scheme affects the experiments the authors tried using a different parcellation scheme with 68-nodes taken from FreeSurfer atlas[17] and grouped into seven networks using the scheme described in this paper[18] and found that parcellations with more nodes in turn gave more accuracy at whole brain level and network level as well.

This experiments was also replicated using the same parameters described by [11] for the whole-brain experiment but was tested on various datasets by authors of [19] and found out that the results were similar to the original paper.

2.2 Analysis of FC with respect to amount of data used

In the above discussed studies the authors used very less data to analyze the Functional connectivity of the brain. To see when there is any change if large amount of data is used the authors of the paper [13] used 10hrs of fMRI data sampled from 10 individuals across 10 different days and 5 cognitive tasks this data was taken from MSC dataset [20]. Following the observations from [11] the authors used 333 parcellation scheme according to the paper [21] and found out that functional connectome is best suited for measuring special characteristics of the brain at an individual level. The authors also infer that there is a slight change in functional network with state change but underlying intrinsic characteristics of the functional network remains same which helps us to uniquely identify a person no matter how the brain is engaged during the process but with reduced accuracy when compared to rest state.

2.3 Analysis of FC based on time

Now that we know that the functional connectome acts as a unique fingerprint for an individual some studies concentrated more on whether the time difference made any changes to the network this can be discussed using the paper [12] where the authors wanted to test the premise that the functional network of the brain remained same in individuals after approximately 1.5 years along with its affect on youth vs adults. The authors also wanted to build on the initial findings from [11] which was discussed in section **2.1** and concentrate more on the sensitivity and specificity of the results obtained. They used classification methods to calculate the AUC and ROC curves. In this way it was possible to account for the false positives and true negatives from the experiments.

The authors created their dataset(discovery sample) by hiring 140(67 male,73 female) participants to the experiments following some strict criteria. The data was taken in the following order 8 minutes of rest state fMRI followed by 40 minutes of task state fMRI scan and end with an 8 minutes rest state fMRI. The same procedure was repeated 1.5 years after on the same participants according to the premise of the experiment. To test whether the inferences from the discovery sample can also be applied to other datasets they used 408 participants to set up the same experiment as replication sample.

From the results of [11] we know that when more nodes were used in the parcellation scheme the identification accuracy was more so the authors followed this paper [21] which proposes 333 nodes as interesting regions of brain.

To know whether the results are generalized they used a separate replication sample and tried to apply their inferences from the discovery sample to it to check whether they get the expected output or not. In the discovery sample, they found out that across the sample identifiability on the same day was very high(AUC 0.94) compared to the identification accuracy after 1.5 years(AUC 0.91). For identification, they did not use the same procedure as [11] but wanted to see how feature selection helps in this scenario. So the authors chose SVM(Support Vector Machines) and elastic net algorithms for classification. They used 75% of the discovery sample as a training sample to extract predictive edges using mentioned algorithms and 25% of the discovery sample as the test set. Then they tested it on a replication sample to know whether the results were generalized or not.

To see results from the network-level analysis the authors used the networks described by the first paper and tried using SVM and elastic net for feature extraction as well. They observed that the predictive edges were overrepresented in frontoparietal, default, and dorsal networks

which were almost similar to the results from the paper [11]. They were able to replicate the same results with high accuracy compared to whole-brain level analysis and when the features from the discovery sample were used, it in turn increased the identification accuracy in the replication sample showing that the results are generalized.

2.4 Analysis of FC in youth vs adults

The authors also wanted to know whether age played any role in the functional network of the brain so the volunteers for the experiment were divided into two classes youth(¡ 18) and adults(¿= 18). It was observed from the fMRI scans in rest state the identification accuracy remained the same in youth and adults on the same day and a reduced accuracy level compared to same day scan after 1.5 years. Furthermore, they also found that the predictive edges remained the same in both youth and adults stating that the reduced accuracy was not due to developmental changes. Significant cognitive development occurs through adolescence [22] but the stability in the identification accuracy also implies that some network-level parameters define an individual's uniqueness. The author of this paper [19] also ran same experiment but concentrated more on youth and 4 different longitudinal datasets and found that stability in FC was due to some underlying network level inferences (fronto-parietal regions) similar to results by [11].

2.5 Role of plasticity in FC

To further test the effect of time the authors of [12] repeated the experiment for greater than 18 months (1.5 years) for a small sample and found out that they could still identify an individual but with reduced accuracy. The authors speculated that the reduced accuracy might be because of the greater noise between the two scans (2 years apart) and also might be because of some plasticity of the brain or a combination of both.

Some of the recent research suggests that the plasticity of the brain alters the topology of the functional connectome in our brain this might be due to the experience gained during the time and the changes that are undergone during the time. According to the authors in the paper [14] they tested the role of plasticity in adults due to career experience using sailors as examples and found out that auditory, visual, executive control, and vestibular function-related networks showed major change through time and these are generally linked to sailor's experience in withstanding continuous auditory noise, maintaining the balance, locate one's position in 3-D space at sea and following orders respectively. This is one of the open questions of the field that requires more research.

3 Common settings followed in the experiments

It is always important for any research project to follow some restrictions which help mitigate extraneous variables to affect the results of the experiments. In this part of the section, discussions are made regarding some of the similar settings imposed by authors from [11], [12], [13],[14]. In all the cases since non-invasive technology is used to extract information from the brain, it is prone to have some external noise, and to reduce this all the authors mentioned in their experiments that the head movement is one of the major issues that might affect the results of the experiments. So extra care was taken by them to remove the data that had a lot of head movement.Especially the authors of paper[12] experimented with youth so there were a

lot of cases where the head movement caused different results but after removing the corrupted data they got unbiased results. The preprocessing step was different for some experiment as the approach was different but in most cases, common pipelines for preprocessing was used specified in [23] which helps maintain consistency in the fMRI image data before it was used for experiments.

4 Summary

To summarize the review paper started by explaining what connectome is followed by short explanation about brain parcellation. The review paper tries to answer the questions from introduction by first critically analyzing about the functional connectome and its nature of uniqueness at an individual level[11]. Then to further support the results the paper provides observations when various parameters of the experiment were changed. For further in depth analysis the problem is approached from new perspective by changing from node level analysis to network level analysis to find out that some parts of the brain contribute most towards identification of a person.

A new paper[12] is then introduced that helps to solve some of the problems that are not answered in section **2.1** it discusses about the validity of the results from previous literature and tries to answer the question of stability(how long does the functional connectome stay unique for person to identify them from others). Here, some machine learning techniques are used for feature extraction purpose and also as a classification algorithm to find whether the results are generalizable or not.

Now the question is answered from the perspective of age and how it effects the functional connectome in youth Vs adults. Some sound arguments were presented [14] which also takes into account how the plasticity of the brain plays a role in such scenarios.

5 Conclusion and Future Scope

To conclude different authors approached the problem from different perspectives to better understand how the functional connectome changes with respect to test subjects, time, age etc. It is observed that the functional connectome has some intrinsic features that do not change for an individual but the reduced accuracy when comparing the functional network might be due to variance from other parts or networks of the brain. It is also an open question in the field whether the plasticity has a huge impact on the networks or not. From the papers discussed it is evident that a standard framework can be created in future experiments and also by understanding the functional connectome it helps us to take a step closer towards personalized medicine for neurological diseases.

There are few limitations in the field for example there are no studies that try to fully explain the role of plasticity of the brain this could be solved by doing experiments with huge sample size i.e comparing data from huge samples of adults and huge samples of youth. Since it is a new rising field and it is well established that understanding brain connectomes helps us to better understand some neurological diseases and how non similarity in functional connectome may lead to a person developing psychiatric conditions like schizophrenia, dementia in early stages of youth. According to the authors of the paper [24] it is observed that there are group level evidence showing abnormalities in structural and functional networks for people with mental disorders. There are some individual level studies taking place for example the authors of the

paper [25] found out that the fingerprinting ability(uniquely identify a person) has reduced for patients with schizophrenia but was not able to decode any helpful features as to why the result was obtained.

The experiments that defined the stability, generalizability of FC paved a path in analyzing cognitive states of the brain. All the research that is currently taking place use machine learning and deep learning algorithms to find important features of networks in the brain and also there are studies that use ML to classify the state of a person.

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