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Chapter 3

Brain Connections – Resting State fMRI Functional Connectivity

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Additional information is available at the end of the chapter

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1. Introduction

With the introduction of electroencephalography (EEG) in 1930, researchers began to explore spontaneous activity in the brain by recording the individual, independently of any task. Subsequently, evoked potential studies, where electrical potentials were recorded at the onset of a stimulus, marked a milestone in brain research. Utilizing such methods coupled with experimental psychology, researchers were able to explore task-related brain activity. These early methods paved the way for new approaches to exploring brain function.

With the advent of blood oxygen-level dependent contrast (BOLD) measurements using MRI, the first fMRI study was published in 1992 by Kwong and colleagues [1]. Within two decades, fMRI has been an indispensable tool in the investigation of cognitive function of brain. Currently fMRI studies comprise 43% of all fMRI publications [2]. At the time, it was believed that when a stimulation paradigm is used to explore brain function (task-based fMRI), only a small percentage of the energy utilized by the brain is actually measured.

The brain represents 2% of our entire body mass. Despite this, studies have shown that the human brain is responsible for approximately 20% of the energy we consume. Additionally, when one performs a specific cognitive task that involves attention or reflection, the brain only uses 5% of its total metabolic expenditure [3, 4]. Yet, how does the brain expend the majority of its energy?

In 1995, Biswal and colleagues observed that regions that are co-activated during a task are correlated in their activity in the absence of a task [5]. This observation led to the conclusion that intrinsic activity in the brain is a major source of energy expenditure. Up to that point of time, spontaneous low frequency BOLD fluctuations were discarded as noise in task based fMRI studies. These signals were considered to be crucial to understanding the intrinsic activity of the brain.

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Resting state fMRI relies on the assumption that spontaneous low frequency BOLD fluctuations are a measure of intrinsic activity in the brain. Furthermore, the robustness of functional connectivity analysis as a tool that reflects fundamental aspects of brain organization through various cognitive states is another assumption that underlies this methodology. Early methods of clinical observation and measurement were essential to the development of the neurosciences. With the emergence of these techniques in the 19th century, their application to the investigation of certain diseases and syndromes led the conclusion that certain areas of the brain are correlated with specific higher executive function, such as language and memory [6].

However, it is currently understood that higher cognitive functions are not localized to specific areas of the brain, nor are they organized in a topographic fashion. Higher mental processes are based on the cohesive and dynamic interplay of a complex set of functional systems and cortical networks. To explore these dynamic and cohesive networks, the utility of fMRI in linking a specific task with a specific pattern of brain activation (a set of co-activated areas) is indispensable. For example, studies that sought to demarcate cortical regions of face recognition and mathematical computation demonstrated that such higher mental functions require the integration of distributed cortical regions. Thus, cognitive activities of higher mental order are not region specific, but are the result of the dynamic interplay of a diffuse set of cortical areas and their underlying anatomical connectivity. Consolidating the knowledge gleaned from various studies that focus on patterns of neural Activation is a serious challenge that the neuro-scientific community faces today. Studies of neurological and neuropsychiatric diseases [7] have substantiated that dysfunction in the brain is not due to a focal lesion or the alteration of a single brain area, but due to the failure of more widespread and diffuse systems. Schizophrenia and autism, for example, are currently regarded as complex disorders of connectivity between components of large-scale brain networks. The human brain is composed of approximately one billion neurons that establish a complex underlying network of structurally and functionally interconnected regions. Complex cognitive processes are possible as a result of the transmission of information between different functional areas of the brain [8]. By exploring the neuroanatomy of the brain and the underlying connectivity of different functional areas, we can afford new insights on the organization of the human brain.

2. Brain connectivity: Basic concepts

To better understand the concept of functional connectivity, it is necessary to differentiate between functional connectivity and structural connectivity. We define the two concepts in the sections below.

2.1. Structural connectivity

Structural connectivity is defined as the set of physical connections between neural units. Physically, anatomical connections are relatively stable over short time scales (seconds or minutes), however, on larger time scales (days) they are subject to significant morphological

changes due to neuroplasticity. Nonetheless, the acquisition of these 'static' images of the microstructure underlying the brain has wide implications on neuroscientific and clinical questions. Currently, structural connectivity is investigated via methods that span axonal tracing, histology and MRI. Technical progress in high-resolution MR has paved the road for the examination the human cortex in vivo at resolutions of up to 300 microns. These scales are approaching the resolutions obtained by histological analysis, which allow for the verification of information obtained with cytoarchitectural maps for better division of the images obtained by MR. [9]

Early work by Hahn [10] focusing on the effects of molecular diffusion on the magnetic resonance signal marked a landmark in nuclear magnetic resonance research. Within a decade, pulsed magnetic field gradients for the measurement of molecular diffusion were introduced by Stejskal and Tanner [11]. Later, Le Bihan was able to incorporate diffusion sensitizing magnetic field gradients into MRI [12]. This led to a novel method that had wide applications in the analysis of the microstructure of the brain (Diffusion MRI). Diffusion MRI is based on the simple idea of tracking the random walk of water molecules in the anisotropic and confined space of axonal fibers. In 1994, Basser proposed a simple method to quantify the Brownian motion of water molecules using tensor models (Diffusion Tensor Imaging) [13]. While others models of quantifying diffusion were proposed, Basser`s single tensor model is the most popular. Further research on the application of the tensor model led to the introduction of tractography techniques (DTT, Diffusion Tensor Tractography). By tracking the path of the principal eigenvector in a single voxel, researchers were now able to reconstruct various white matter tracts noninvasively. However, the Diffusion Tensor models introduced had a limited number of degrees of freedom and assumed that the probability density function was Gaussian. As a result, single tensor diffusion imaging is intrinsically limited in the analysis of voxels with multiple fiber populations, which could be crossing, fanning or kissing [14]. Although multi-tensor models (high angular resolution diffusion) and Diffusion Spectrum Imaging methods were introduced to overcome these limitations, assumptions persist in these methods, making it difficult to explore neuroanatomy to a high degree of accuracy.

To investigate the accuracy of these methods, several groups have attempted to compare noninvasive fiber tracking with gold standard methods [15,16]. Lawes performed a direct comparison between atlas based reconstruction methods and postmortem classical dissection methods [17]. Tracts reconstructed using the Diffusion Tensor model are accurate to some degree, as they have been applied to the clinical setting.

Nonetheless, although it may provide important information about the structural connectivity between different brain areas, diffusion MRI does not provide a direct measure of functional connectivity in the brain. While diffusion imaging can provide information about the spatial relationship between two areas, it does not provide any information about their temporal correlation. Such information has vast implications for cognitive neuroscience research.

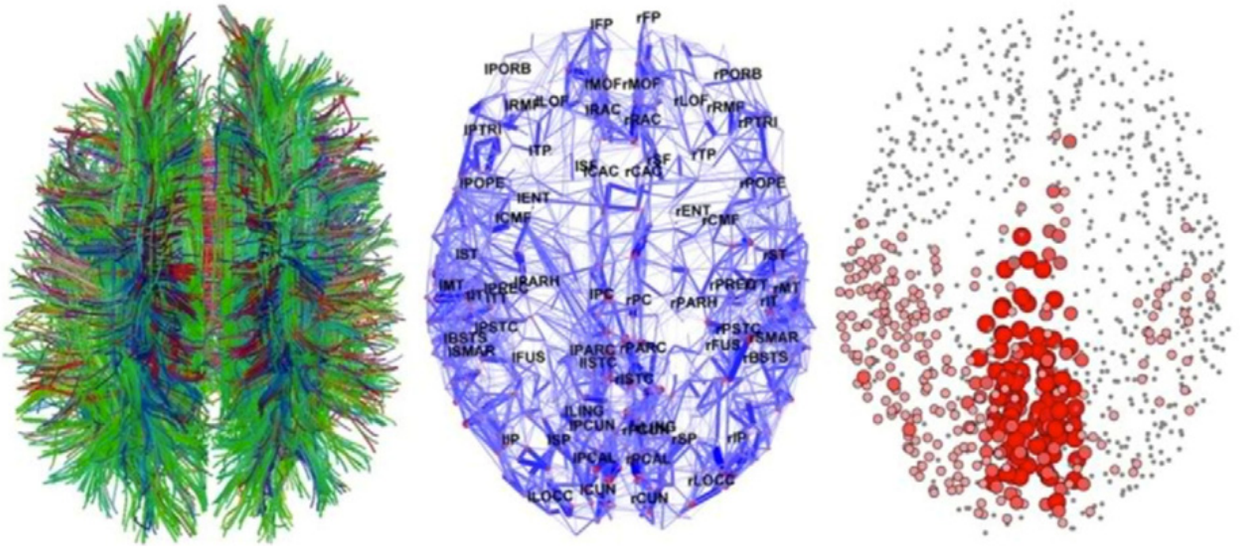


Figure 1. Diffusion Tensor Tractography (left), graph of connectivity (center), functional connectivity (right). Modified from Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS Biology.

2.2. Functional connectivity

Functional connectivity (FC) can be investigated through various analytic methods that include electroencephalogram (EEG), infrared light spectroscopy, task-based and resting state fMRI. By extracting correlation measurements from time series, functional connectivity information can be acquired. Functional connectivity is essentially a statistical concept [18]. Unlike anatomical connectivity, which describes physical pathways of information exchange, functional connectivity describes the correlation of spatially remote areas in the temporal domain. Dependence is calculated between all elements of a system, whether these elements are connected by direct or indirect structural links. Functional connectivity relies primarily on traditional fMRI techniques, but takes advantage of low BOLD frequency fluctuations to examine intrinsic activity in the brain. Functional networks generated using this method have been termed 'resting-state networks'. Approximately 60-80% of brain metabolic consumption is due to the intrinsic activity of these networks.

2.3. Linking structure and function

In order to link structure to functions, one must consider the mechanism by which two spatially remote areas are coactivated at any given time. It is currently unclear how many of the networks detected at rest consist of direct anatomical links between cortical regions. Can areas that do not have direct anatomical links exhibit functional connectivity? White matter tracts can be considered as information highways that allow the exchange of functional information between spatially remote regions. In this context, a high temporal correlation between spatially remote areas must reflect a path of communication. Temporal correlation between two regions implies that there are underlying anatomical links that facilitate information transfer. Recently, studies that utilized both diffusion weighted MRI and resting

state fMRI, have suggested that there is a direct association between functional connectivity and structural connectivity in the human brain [15, 19]. Having a clearer picture of anatomical structure is critical for the analysis of functional dynamics. However, structural connectivity does not provide any information about the temporal organization of information exchange between regions. Therefore, it is important to note that while functional connectivity implies structural connectivity, it does not imply that two areas a directly connected. For example, the primary visual cortex has been shown to have strong functional connections between its left and the right cerebral hemispheres, although underlying white matter links are lacking between those regions [20].

It is observed that the functional interactions and their expression in behavior of the whole organism can profoundly influence the structural patterns through a variety of mechanisms of plasticity so that shows how the structural and functional connectivity are reciprocally linked.

Studies that utilized EEG methods to examine spontaneous neuronal activity have shown similar patterns of correlations exhibited by resting state fMRI. The nature of spontaneous neuronal dynamics is a potential indicator of the presence of a "critical state", similar to a dynamic regime that is characterized by a diverse set of intrinsic neuronal states that provide answers to extrinsic disturbances. These consistent patterns of activation and deactivation of brain regions during the transition from the task and resting state, led to the discovery of a default mode state called default mode network (DMN) that is consistent across multiple studies of rs-fMRI and/or EEG [21-25].

3. Functional connectivity: Resting state fMRI methods

In the following sections, we review several commonly used techniques for investigating functional connectivity using resting state fMRI data. While these methods range across numerous mathematical fields, and are based in various different assumptions about how to understand underlying brain organization, they can fundamentally be grouped into two categories: model-based and model-free methods. In any case all methodologies can lead us to define a brain network as we will see in the following sections.

3.1. Model-based functional connectivity methods

Seed-based analysis is a hypothesis-driven method that is based on a priori decision regarding the region-of-interest (ROI). Functional connectivity is then calculated using the signal from this ROI as the model in subsequent voxelwise analysis.

Another common method used to establish ROIs for seed-based functional connectivity analysis is meta-analysis. This technique is used to summarize the results across several neuroimaging studies in order to establish common regions of activation. Such results then serve to establish a consensus on the location of functional regions and to develop hypotheses for further investigation.

The goal of this analysis is to locate regions consistently activated (if any) on a set of diverse and independent studies, which are related to the same psychological state [26]. This method works basically by counting the number of peaks of activation in the studies presented, comparing the number of peaks observed with a distribution of null to set a criterion of significance. The two most representative approaches to perform such an analysis are kernel density analysis (KDA) and activation likelihood estimation (ALE) [27].

3.2. Model-free functional connectivity methods

By definition, hypothesis independent methods lack a priori assumptions. These methods are especially useful in the analysis of spatially distributed functional connectivity networks, as they are not reliant of localized assumptions [15, 28-36].

The first analysis to study the functional integration used **Principal Component Analysis** (PCA) [15, 37] to decompose fMRI data into a set of mutually uncorrelated components in either space or time. More recently, **Independent Component Analysis** (ICA) has been used to identify components that describe the activity in a widely dispersed network [28-35]. ICA is an extension of the classical methods of Blind Source Separation (BSS). This technique decomposes the time series in order to identify statistically independent components that define functional networks. This technique has the advantage of extracting independent components that may consist of noise signal, such as physiological or movement-related noise. Although this analysis has many advantages and its applicability has opened doors to new possibilities in the study design, the maps generated with this method are usually more difficult to explain in comparison with those generated with the seed voxel analysis, therefore, its applicability has some restrictions and limitations. Different authors have analyzed the methodology of this technique and there are different variations of the method [38, 39]. ICA has been used to explain a better way the large-scale structures that have been detected in several independent studies [15, 36].

Clustering techniques aim to subdivide the data by means of a mathematical algorithm, so that the observations assigned to the same group are more similar to each other than the observations assigned to other groups. In the context of the study of functional connectivity analysis in rs-fMRI, clustering algorithms have been used to perform brain parcellation in groups of voxels or regions that are functionally connected to other regions. It should be noted that clustering techniques applied to fMRI data are having a good acceptance both in the detection of functional connectivity networks and in the architectural (anatomical) subdivision of the brain [36].

The first application of clustering techniques to resting state functional data was performed by Cordes et al [40]. Firsts attempts to employ this technique were limited due to the computational complexity [41, 42]. Recently, more sophisticated studies have been performed [43, 44] that have enabled identification of large-scale networks that agree with those found in other studies [44].

Still, we should take into account some limitations to the technique. The most important is that most clustering techniques require a priori selection of the number of clusters (K), which will partition the data [36]. Since this value clustering (K) is unknown, multiple solutions are usually calculated using a metric that predicts the "goodness" to determine the optimal number of groups for that data set.

There is no single measure or an optimized solution, so different methods are used. Ultimately, it is unlikely that the clustering is entirely independent of the initial partition decision (K) determined by the subjectivity of the user, since it must evaluate the appropriateness of pooling the results compared with networks of functional connectivity well known. It can be concluded, therefore, that this technique also depends on the subjectivity of the observer when describing the goodness of a grouping, as well as ICA.

3.3. Brain networks and graph theory

In 1998 Watts and Strogatz introduced the concept of small-world network [45]. There are certain reasons, both empirical and theoretical, to understand the brain as a small-world network [46] because the brain supports both distributed and modular processing (linked to the concepts of functional segregation and functional integration). Considering the cognitive processes under the network architecture, it is more efficient when exchanging information at various scales: a high clustering allows a modular processing, while further distances allow for distributed processing. Thus, small-world networks maximize the efficiency of parallel processing and minimize the cost of communication between modules of nodes, as well as being tolerant to failures.

Graph theory is the field of mathematics that is used to characterize various aspects of network structure. In functional connectivity analysis, the application of graph theory aims to ascribe nodes to various regions of interest, and generates links or arcs between them. This approach makes it possible to explore functional connectivity networks using tools that characterize typical properties of networks, for example the study of efficiency and modularity.

Applying graph theory to resting state fMRI data involves assigning nodes to various regions of interest. A functional connectivity graph is generated once edges are assigned to connect nodes that have correlation values above a certain threshold. An important feature is to study "the path", which is defined as a sequence of connected nodes. Path length between two nodes is defined as the number of edges passing through node i to a node j. The distance between two nodes of a graph is the minimum length among all possible paths connecting these nodes. Degree of a node is defined as the number edges that are connected to it.

Two types of metrics are used to characterize graphs: local and global metrics. In local metrics, values are assigned to each node individually, while in global metrics, values characterize the graph as a whole.

A very important metric is the degree of distribution of a graph P(k). This metric provides information on the number of nodes that offer a high degree of centrality. Various studies

have shown that the scarcity of these nodes can be related to cognitive decline as observed in Alzheimer's patients.

A complex network can be represented mathematically by edges and nodes [47]. Mathematically, nodes represent different parts of a system, and the relationship between two nodes is represented by an edge. Applying these mathematical concepts to the brain, nodes represent different areas of the brain, while edges represent anatomical, functional or effective connectivity's between these nodes. Utilizing such tools, we can construct (i) anatomically based networks of white matter tracts; (ii) functional connectivity maps representing patterns of correlation between BOLD signals; and (iii) effective networks representing causal interaction patterns between brain areas. All three methods of network depiction can be represented by adjacency matrices. In these matrices, rows and columns represent nodes, while each array element (i, j) represents the interaction between two nodes i, j.

Criteria for the selection of nodes and edges to represent cortical networks often combine methods from anatomical parcellation schemes and connectivity measures. Nodes must represent brain regions with consistent patterns of connectivity, since only similar patterns of fragmentations can be compared. Weighting of edges is interpreted differently in different connectivity models. In anatomical connectivity modelling, weighting is interpreted as a measure of the density of the anatomical tracts. While in functional connectivity models, weighting indicates the magnitude of a correlation between brain areas. And in effective connectivity models, weights may indicate causal interactions. By thresholding weights of connections, networks could be trimmed to establish the topology of significant links. The possibility of directionality in the edges makes it possible to represent anatomical and effective models, while functional models can be perfectly modelled by non-directional arcs.

Functional segregation refers to the involvement of specialized regions or networks in specific functions. Segregation measures are important as they seek to quantify clusters in given network. A basic strategy is to divide a network into subgroups, minimizing the number of edges within a group and maximizing the number of edges outside of a group. Utilizing such means, we can divide a network to be able to analyse a networks modular structure.

Certain areas of the brain that act as hubs are crucial to the functionality of given networks. In order to quantify this importance there are measures of centrality for the network. The degree of a node can be used as a simple measure of the centrality of a node. Other more sophisticated measures can also be used to quantify centrality. Many centrality measures are based on important hubs that play a role in various networks. Measures of centrality have different interpretations depending on type of network under study. A central node in an anatomical network allows the assignment of structure to function between distant regions. Such central anatomic nodes decrease values of centrality in functional networks.

Here we conclude that the analysis of complex networks has equipped use with necessary tools to examine anatomical and functional networks of the brain, paving the way for the possibility of quantifying many of their parameters.

4. RS-fMRI in cognitive neuroscience

It was in 1995 when Biswal and colleagues observed that a significant fraction of supposed noise showed organized patterns consistent with known brain systems [5]. Biswal's work aimed to examine patterns of neural activity of the motor system, and for that, experimental subjects were asked for a standard task of finger opposition and then compared to a rs-fMRI without asking them to do something. As Biswal initially demonstrated, the left and right primary motor networks are correlated. This suggested that these areas are functionally connected and that the process of information transfer between them is on-going [7, 39]. Later, groups were able to replicate these results and further demonstrate correlations between primary visual networks, auditory networks and higher order cognitive networks [3,7, 48-51].

4.1. Adquisition

Advantages of employing resting state functional connectivity analysis in cognitive neuroscience studies include:

1. **A brief period of time of acquisition** (minutes) provides an expanded application to the clinical setting. One of the most frequently cited motivations for using resting state functional connectivity in clinical studies, is that it allows for increased sampling of patient populations, since (i) it requires a brief acquisition period and (ii) has no specific stimulation paradigm. This allows the patient to remain rest, or asleep or under the influence of anesthesia. The absence of a stimulation paradigm in this case, is especially important to the sampling of patient populations with neuropsychiatric disorders.
2. **Computation**: Several resting state functional connectivity methods are available for analysis of neural circuitry in vivo. In contrast, using task-based fMRI, we are only afforded connectivity information about the activated regions only.
3. **Simple design**: (baseline acquisition). Resting state studies may offer a better signal to noise ratio than conventional task-based approaches.

4.2. Networks identified using resting state functional connectivity

A resting state network of particular interest is the **default mode network (DMN).** This group of brain regions is active during rest and deactivates during most externally oriented tasks [7, 52]. This component has been studied in different ways, the main interest of past studies that implemented model-dependent method (seed voxel techniques) [5, 52] as well as independent component analysis (ICA) [29].

Compared with other networks, the DMN is unique in the direction of its response to task performance, which probably relates to its baseline level of neuronal and metabolic activity and its role in brain function. The DMN is not unique, however, in demonstrating correlated intrinsic activity; multiple networks exhibit coherent resting state activity that persists across different states. The default mode network is one of the most robustly identified and extensively investigated resting state networks that involves a set of regions that routinely decrease their activity with tasks that demand attention [3, 7, 52]. Interestingly, this network

has also been found to be negatively correlated with regions that tend to increase their activity during attention demanding tasks. Other identified networks include a self-referential system engaging the medial prefrontal regions; a posterior network involved in visual processing; an attention network engaging superior frontal and parietal cortex; a superior temporal system; and a network-engaging precentral and postcentral cortex [3, 7]. The most consistently reported resting state networks include the primary sensorimotor network; the primary visual and extra-striate visual network consisting of 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 consisting of precuneus, medial frontal, inferior parietal cortical regions and medial temporal lobe [53].

Given the success of resting state functional connectivity for probing the brain's functional architecture in normal subjects, it is a great benefit to employ this technique towards the investigation of dysfunction in the brain. A review by Fox and Greicius [8] highlights advantages of examining the resting state signal for clinical applications and discusses methodological issues that need to be resolved to facilitate translational applications of rs-fMRI. A number of clinical applications are already emerging as emphasized by the studies of functional connectivity in premature children [54], adolescents with schizotypal traits [55], major depression, and aging [56]. Two recent reviews detail the large number of studies that have utilized resting state fcMRI to study various neurological and psychiatric conditions [4, 57].

4.3. Networks involved in neurological and psychiatric diseases

The functional connectivity of the DMN has been linked to core process of human cognition such as the integration of cognitive and emotional processing [7], monitoring [58] and mind-wandering. As a result, analysis of the connectivity patterns of the DMN is especially important in examining cognitive dysfunction in neurological and neuropsychiatric brain disorders [57, 59]. DMN alterations have been reported in a number of neuropsychiatric diseases.

It has been shown that the DMN exhibits decreased connectivity patters in patients with **Alzheimer disease** [60]**,** decreased correlations within the DMN including hippocampi, decreased anticorrelations with the DMN, and reduced local connectivity as reflected in clustering coefficients, in which parts of this network have been clearly implicated.

Schizophrenia has been marked as a potential disconnection disease [61]. Widespread functional disconnectivity between brain regions has been suggested to underlie these symptoms [62, 63]. Schizophrenia is known to have aberrant effects on frontal and parietal regions involved with the DMN. Resting state fMRI studies have reported a decrease in the functional connectivity between medial frontal cortex and precuneus in schizophrenic patients [64]. Additionally, diffusion tensor imaging studies have reported diminished white matter integrity in patients with schizophrenia [65]. Specifically, a decrease in white matter integrity was observed in the cingulum tract, which is known to be interconnected with DMN regions MFC and PCC [50, 57]. Therefore, symptoms of patients with

schizophrenia can be attributed to alterations of the functional connectivity of the DMN. Moreover, studies have also marked spatial differences in the default mode network in schizophrenia patients together with significant higher frequency fluctuations in default mode regions, as well as hyperactivity and hyperconnectivity of the default mode network in patients in the early phase of schizophrenia [64]. These studies suggest an important role for the default mode network in the pathophysiology of schizophrenia.

Altered functional connectivity patterns have been reported in other neurological disorders. For example, in **multiple sclerosis (MS)** a decreased functional connectivity in the primary motor has been established. This has substantiated studies that showed decreased microstructural integrity of the callosal white matter tracts [66]. Additionally, in patients with amyotrophic lateral sclerosis (ALS), ICA analysis has suggested a decrease in functional connectivity [67].

5. Global initiatives and the Human Connectome Project

There has been a long standing interest in the unrestricted sharing and access of functional neuroimaging data within the neuroimaging community. Inherent within the methodology of task based fMRI, the complexity of conforming task paradigms across different acquisition sites limited the potential of having such an open access platform. However, with the introduction of the unique methodological approach of resting state fMRI, a new era in open access data sharing was ushered. Most notably, a data sharing consortium - the 1000 Functional Connectomes project (fcon_1000.projects.nitrc.org) - composed of various groups from all around began this initiative in 2009. The fcon1000 project aggregated and publicly released over 1200 resting state and anatomical MRI datasets acquired at 33 sites around the world. Within the first six months, the release generated over 9000 download from 78 countries. The benefit of unrestricted data sharing on the advancement of neuroimaging is self-evident. Researchers with the resources to acquire data can ensure that their resources are most widely used, while those researchers who prefer to focus on data analysis can do so. Such initiatives had wide implications on the neuroimaging community. Since large sets of data are now freely accessible, the valued commodity of the imaging community is no longer the data itself, but the analytic tools and approaches of interpretation and analysis. This new paradigm of unrestricted data access will be an integral part of the future of brain research. The human brain is usually divided into several hundred areas that exhibit highly specialized function. Cortical and subcortical regions of divergent function exhibit distinct cytoarchitecture when viewed under a microscope. As the human brain develops, mechanisms of axonal guidance allow the projection of millions of axonal fibbers to target destinations. In the process, a complex network of information processing pathways is formed.

The Human Connectome Project (HCP) [68] is an ambitious five year initiative that was launched in 2010. Its main objective is to build a network map of the human brain to shed light on its structural and functional connectivity. HCP leans on the general facet that the function of a system is determined by its structure. By elucidating the complete underlying

structure of white matter pathways, we will be able to glean significant information about the function of this composite organ.

The term *Connectome* was introduced by Olaf Sporns in analogy to the human genome. An approach that is more elaborate than mapping Connectomes, is mapping Synaptomes of the brain. Such an effort would require imaging synaptic clefts at ultra-structural levels of resolution. This endeavour is currently out of reach of the methods we possess today, as it necessitates acquiring images of proteins and neurochemicals that govern the various biochemical pathways of all synapses. Nonetheless, by relying on simple models systems such as *Caenorhabditis elegans* – which has a total number of 302 neurons – we can examine the feasibility of such a project.

Such mapping undertakings would provide considerable information to solve mysteries of brain function. Connectivity in the brain can be studies at three levels of analysis. Combining information from macroscopic, microscopic and nanoscopic levels of analysis, would have wide implications on appreciating the full structural map of the brain.

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