2
Literature Survey

2.1 NETWORK NEUROSCIENCE

Brain is one of the most intricately organized systems that exhibits functional repertoire critical for survival of organisms. Its complexity arising out of cellular circuits and molecular orchestration makes it extremely difficult to find laws governing its structure and function [Herculano-Houzel, 2009]. While advances in molecular biology have provided insights into functioning of individual neurons, better understanding of how tiny electrical impulses, elegantly orchestrated by a group of neurons, enable a living system to interact with its environment has been out of reach [Eric R Kandel, Dudai, and Mayford, 2014]. This lack of systems-level understanding of brain is an obstacle in finding ways of its control [Edward T Bullmore and Bassett, 2011; Park and Friston, 2013; Sporns, 2013b]. Advances in techniques for mapping brain and ways for more precise ways of external control are opening up new avenues in brain science. For example, functional brain imaging, non-invasive brain stimulation, and optogenetics have provided unprecedented abilities to record and perturb nervous systems [Fenno, Yizhar, and Deisseroth, 2011; Orrison, Lewine, Sanders, and Hartshorne, 1994; Rossini et al., 1994]. Using the abstract formalism of graph theory, brain mechanisms could be modeled as networks in search of general principles underlying its function and control. This integrative approach has been dubbed as 'network neuroscience'.

In this thesis, taking an integrative approach to brain, we asked questions delving on systems biology of structural and functional brain networks. We study the *C. elegans* neuronal network, to find their driver neurons using controllability analysis and characterize them based on their phenotype and genotype. Asking questions about their structural constraints that play role in specifying prevalence of motifs and nature of control, we propose a distance constrained model. We find distance constrained rewiring to be a key feature for maintaining robust control in CeNN. Further, by applying the concept of structural balance, we show that inhibitory synapses are central to achieve the observed balance in CeNN. In these investigations we invoke structural connectivity of neurons, features of neurons and synapses as well as gene level details. Beyond structural networks, we constructed graph theoretical models of brain functional networks to identify topological biomarkers that characterize activity patterns of schizophrenia. Using features from different layers of nervous systems, as depicted in Figure 1.2, our studies provide new insights into brain structural and function.

2.2 NETWORKS IN BRAIN

Neural networks are web of interconnected neurons through which they interact and produce paths of activations leading to behavior [Thomas and McClelland, 2008]. These paths consist of several axon terminals which are connected via synapses to other neurons. The activation patterns can be seen as functional neural circuits which regulate its own activities via feedback, thus providing substrate to produce response in accordance with external stimuli [E.R. Kandel et al., 2000]. For example, an obnoxious stimuli suggesting urgency and dangerous situation for the animal are detected via specialized nerve cells called sensory neurons. These receptors then send signals which are relayed to muscles to get away from the harmful stimuli. This simple example demonstrates evolution of structural features in brain networks (Figure 2.1).

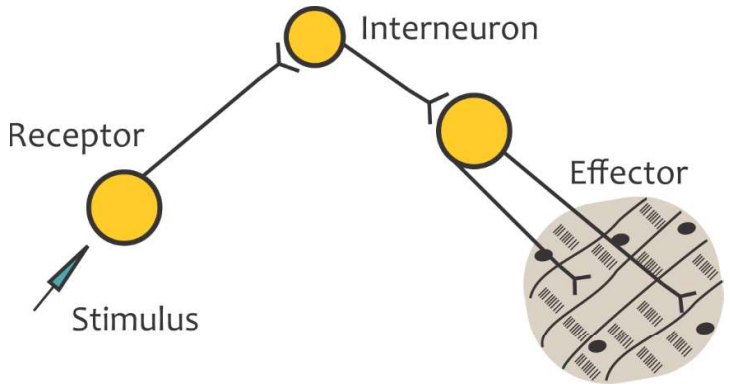

Figure 2.1 : The structure of a simple neuronal circuit required to respond to an external stimulus.

These connections between neurons or interconnected neuronal regions in higher animals display spatial as well as temporal characteristics. Spatial layout of the nervous system is represented by the structural connectivity of the neurons. Activity-dependent temporal synchrony between brain regions are captured by functional brain networks [Park and Friston, 2013; Sporns, 2013a]. The study of these structural and functional brain networks can offer insights into emergent properties of the nervous system [Rubinov and Sporns, 2010; Sporns, 2011].

Such studies involving the structure and dynamics of nervous systems require the knowledge of neuronal connectivity. It is difficult to assess the structure of large scale neuronal networks found in humans or other vertebrates [Sporns, 2013b]. The available data of structural connectivity in higher organisms are course grained and not comprehensive. On the other hand, it is easier to construct detained neuronal wiring diagram for invertebrates. The nematode *Caenorhabditis elegans* is the only example of a nervous system for which a complete, fine-grained map is available [Hall and Russell, 1991; Oshio et al., 2003; White, Southgate, Thomson, and Brenner, 1986]. Availability of high resolution details of anatomy and developmental processes in *C. elegans* further facilitates mathematical modelling and computational analysis. Thus *C. elegans* comes out as an interesting model system.

The topological layout of *C. elegans* neuronal connectome has been mapped by representing the nervous system as a graph in which each node denotes a neuron and each (directed or undirected) edge denotes a synaptic connection between neurons [Beth Li-ju Chen, 2007; Choe et al., 2004]. The *C. elegans* neural network is a small-world network possessing a combination of high local clustering of connections between neighboring neurons and short path lengths between neurons [Towlson, Vértes, Ahnert, Schafer, and Bullmore, 2013]. This network achieves efficient communication with sparse connectivity (low synaptic density) and decreased energy consumption [Ahn, Jeong, and Kim, 2006]. Similar to many other real world networks, this network is also known to be robust to random errors [Ahn et al., 2006; Itzhack and Louzoun, 2010; Pérez-Escudero and de Polavieja, 2007].

While comprehensive data of structural connectivity in human brain remains elusive, its functional connectivity can be mapped using non-invasive techniques like EEG and fMRI. These techniques provide a platform for finding temporal activity correlations between parts of the brain. By virtue of its structure human brain exhibits a wide repertoire of functions [Park and Friston, 2013]. It is proposed that the resolution of 'connectivity-to-function paradox' may reside in brain's functional network architecture [Eric R Kandel et al., 2014; Sporns, 2011; E. Tang and Bassett, 2017]. Recent analyses of human functional brain circuits suggest the presence of small-world nature and scale-free connectivity distribution [Achard, Salvador, Whitcher, Suckling, and Bullmore, 2006; Meunier, Lambiotte, and Bullmore, 2010; Rubinov and Sporns, 2010; Cornelis J Stam and Reijneveld, 2007]. It has been hypothesized that neurological disorders arise due to

change in underlying structural or functional schema [Anderson and Cohen, 2013; Rish et al., 2013; van den Heuvel and Hulshoff Pol, 2010]. One powerful approach to examine these connected regions based on activity correlations between the regions of the brain is functional Magnetic Resonance Imaging (fMRI) [K J Friston, Jezzard, and Turner, 1994; Karl J. Friston, 1994]. Using Blood Oxygen Level Dependent (BOLD) data from fMRI imaging provides an indirect measure of brain activity. The functional organization of brain could be understood by studying temporally correlated activity between brain regions. Resting state functional MRI (R-fMRI) is a relatively new and powerful method for evaluating regional interactions that occur when a subject is not performing an explicit task. The spatial patterns of R-fMRI correlations are stable, i.e. they are similar across multiple 'resting' states, such as eyes-open, eyes-closed, and fixation, and also across individuals and sessions [Biswal et al., 2010; Fox, 2010]. Hence R-fMRI can be utilized for comparison between individuals for detecting variations in activity over time, which may help in diagnosis or study of progression of a neuropathology.

In this thesis we investigated structural and functional networks of the brain. For the study of structural networks we have considered neuronal network of *C. elegans* (Chapter 4 — Chapter 7); whereas R-fMRI data from humans was used to analyze functional brain networks for finding graph theoretical markers of schizophrenia (Chapter 8).

2.3 NETWORK MOTIFS

Real-world networks are known to be characterized with global properties such as small world nature, by virtue of compactness and high clustering [Dehmer, 2011; Ravasz and Barabási, 2003; Watts and Strogatz, 1998]. They are also known to have scale free distribution of connectivity with presence of hubs [Albert and Barabasi, 2002]. Neuronal networks tend to follow these broad topological features, while presenting with some exceptions [Biswal et al., 2010; He, Chen, and Evans, 2007; Towlson et al., 2013]. For grasping the functional specifics, it is necessary to look beyond these global properties [Alon, 2007b; R Milo et al., 2002; Sporns and Kötter, 2004].

Nervous systems are integrated devices made up of several neurons. Neurons have pronounced tendency to make synaptic connections within the local neighborhood [Beth L Chen, Hall, and Chklovskii, 2006; Gushchin and Tang, 2015]. This results in high clustering and formation of circuits with unique pattern of connectivity, the sub-structures. Some sub-structures are known to be over-represented in real-world networks compared to their random counterparts, and are referred as motifs [R Milo et al., 2002]. Presence of local patterns was observed in one of the early studies while construction of neuronal wiring diagram of *C. elegans* [White et al., 1985]. In a pioneering study by Milo et al., and subsequent investigations, have reported overabundance of certain three and four node motifs (Figure 2.2) [Beth L Chen et al., 2006; R. Milo et al., 2004; R Milo et al., 2002; Reigl, Alon, and Chklovskii, 2004].

In biological systems, such as metabolic and gene regulatory networks, motifs are known to contribute to biological functions [Alon, 2007b; Mangan and Alon, 2003]. However, the relevance of motifs in brain networks is under constant interrogation. The biological relevance of neuronal motifs could be understood by considering examples of evolutionary forces. Animals need to appropriately respond to different situations. For example, they need to move their body when they sense food, and move away in the presence of danger. Thus, the animal needs to continuously monitor and assess its environment so as to suitably respond to external stimuli.

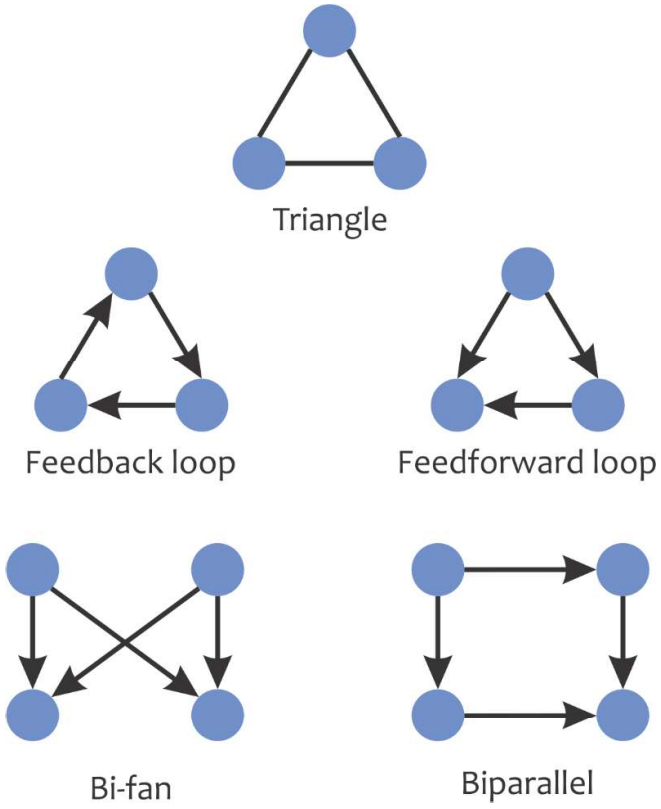

Figure 2.2 : Different network motifs prevalent in biological systems. The feed-forward loop, bi-fan and biparallel are over-represented, whereas feedback loop is under-represented in gene regulatory networks and neuronal connectivity networks [R Milo et al., 2002]. Figure adapted from [Tran et al., 2013].

Neuronal network form the underlying information processing system that process the external stimuli as well as respond to it. Sensory neurons capture the signals in the form of action potential and learn by strengthening/weakening of neuronal pathways (synaptic plasticity). This gives rise to topological patterns in structural connections (motifs) [Beth L Chen et al., 2006; E.R. Kandel et al., 2000] Thus in principle, different classes of motifs can support different modes of information processing and their distribution can be of adaptive value [Ron Milo, Itzkovitz, Kashtan, Levitt, and Alon, 2004]. It has also been suggested that motifs facilitate synchronization in networks [D'Huys, Vicente, Erneux, Danckaert, and Fischer, 2008; Vicente, Gollo, Mirasso, Fischer, and Pipa, 2008]. In this thesis we studied the role of synaptic plasticity in modulating Feed Forward Motifs in *C. elegans* neuronal network which renders robust control response to the network.

2.4 STRUCTURAL CONTROLLABILITY

Structural controllability is an engineering concept from control theory which deals with nature of control in a networked system and aims to identify points of interventions through which the system could be controlled to achieve a desired state. A network is said to be controllable if it can be driven from any initial state to a desired final state by providing suitable inputs in finite amount of time [Lin, 1974]. This implies that a dynamical system could be nudged into some of its plausible configurations (states) through external inputs. As a simple example let's consider a linear time-invariant system with state x, state matrix A and input matrix B, such that the state at time t with input signal u can be represented as:

$$x(t) = Ax(t) + Bu(t) \tag{2.1}$$

$x(t) = x_1(t), \dots, x_N(t)$ is the state of the system at time t. The A matrix describes $N \times N$ adjacency matrix. $B = N \times M$ is a matrix that depicts nodes controlled with an input signal $u(t) = u_1(t), \dots, u_M(t)$. The state of such a system is proven to be controllable if and only if the $N \times M$ matrix possesses full rank.

The concept of the structural controllability was first introduced by Lin (1974), which was independently extended by Shields and Pearson (1976) as well as Glover and Silverman (1976) [Glover and Silverman, 1976; Lin, 1974; Shields and Pearson, 1976]. The necessary conditions for a linear time invariant system to be structurally controllable include the requirement that the system is spanned by cacti structure, and is devoid of dilations as well as inaccessible nodes. These have clear graph theoretical interpretations as illustrated in Figure 2.3. In graph $G(V, E)$ vertex V_i is said to be inaccessible if there exists no direct path from the origin. The graph $G(V, E)$ contains a dilation if there is a subset $S \subset V$ having neighborhood set $T(S)$ which is defined as a set of all vertices V_j containing an edge impinging on a vertex in S i.e. $T(S) = \{V_j | (V_j \to V_i) \in E(G), V_i \in S\}$. The origins are not allowed to belong to S but may belong to $T(S)$. $|S|$ or $|T(S)|$ is the cardinality of set S or $T(S)$, respectively.

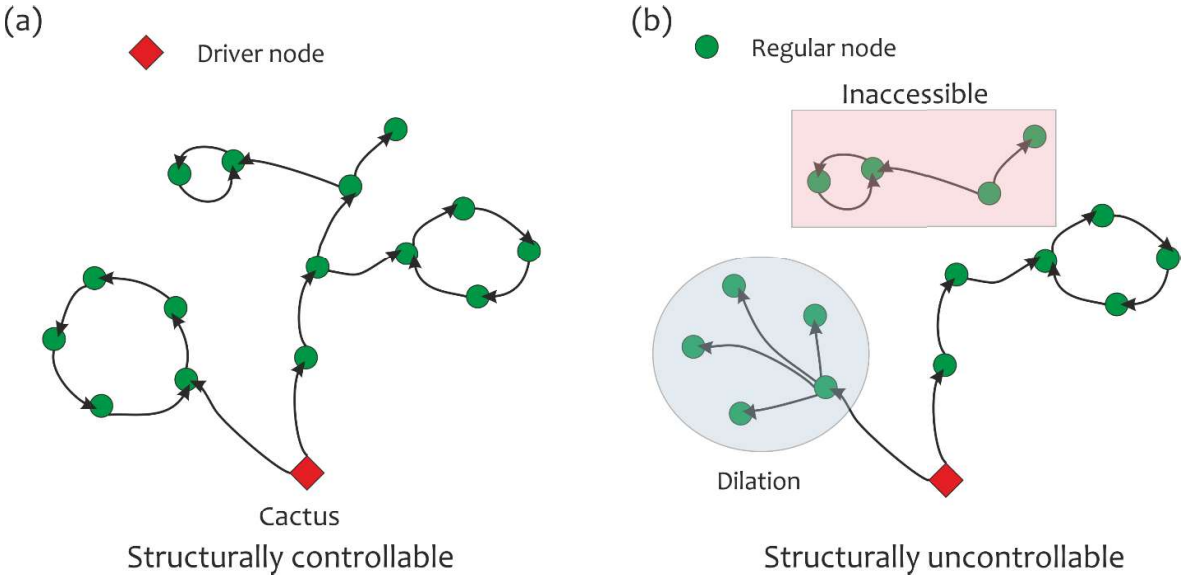

Figure 2.3 : Illustrations explaining structural control in graphs. (a) Structurally controllable cacti structure where the driver node is represented in red. (b) Presence of dilations and inaccessible nodes makes the network structurally uncontrollable.

The benefit of cacti structure is that it lacks dilations and inaccessible nodes, thus making a network controllable through an external input given to a small subset of nodes. These set of nodes capable of driving the state of the network are called as 'driver nodes' [Y.-Y. Liu, Slotine, and Barabási, 2011]. These nodes have property of being downstream of a node which is necessary condition for being controllable [Lombardi and Hörnquist, 2007]. Using graph theory, structural control theory, and statistical physics, it has been shown that minimum number of inputs required to maintain full control over the network can be determined by 'maximum matching' in the network [Y.-Y. Liu et al., 2011]. Matching is a subset of a graph where at least one edge is incident upon each node. Maximum matching set of edges can be defined as maximum number of links which share start or end nodes. These edges are referred to as matched edges. The nodes which are linked by unmatched edges form the minimum set of driver nodes. In an undirected graph matching, M is an independent edge set which is without common nodes. A node is matched if it has a matching incident edge, otherwise it is unmatched. For a directed graph two edges are matching if both are not starting or ending in a common vertex. Similarly, a vertex is matched if it is pointed by a matching edge. Maximum matching is easier to implement in undirected networks. In directed networks the most efficient way to compute the minimum

set of driver nodes is by using a bipartite representation of graph with the help of classical Hopcroft-Karp algorithm. This algorithm runs with a worst case computational complexity of $O(\sqrt{N}E)$, where N is the number of nodes in the graph and E represents the number of edges [Hopcroft and Karp, 1973]. A matching with the maximum size is called a 'maximum matching'. If all the vertices are matched then the matching will be called 'perfect', and it is referred as 'unique' if there exists only one type of matching set. In a perfect matching graph the minimum number of inputs needed for full control of the network is zero i.e. any node in the graph can act as a driver node. Otherwise, it is equal to the number of unmatched nodes.

Identification of the number of unmatched nodes as defined by the Hopcroft-Karp algorithm is computationally inexpensive and is used widely. However it has certain shortcomings: (a) In directed networks this algorithm cannot tackle cycles of odd length. (b) The matching presented is ambiguous and is sensitive to the initiation point.

Since the brain networks, studied in this thesis, are directed (and hence may contain cycles of odd length) and obtaining exact set of driver nodes is important for deriving biological interpretations, we implemented an algorithm which finds exact set of driver nodes. In 1990, Pothen and Fan presented a two-step algorithm for finding an augmenting path to update the minimum set of driver nodes [Duff, Kaya, and Uçcar, 2011; Pothen and Fan, 1990]. Although finding augmented path makes its worst case computational complexity $O(NE)$, this algorithm is still efficient compared to the brute force method which has a complexity of $O(2^N - 1)$.

Brain networks are particularly interesting from the perspective of control, as its underlying architecture predisposes certain components to specific control actions [Gu et al., 2015; E. Tang and Bassett, 2017; Y. Tang, Gao, Zou, and Kurths, 2012]. Brain is a system of neurons and neuronal ensembles or regions (nodes) that are interlinked via anatomical bridges (edges). This underlying architecture of brain is responsible for its function, development, and disorders [Danielle S Bassett and Bullmore, 2009; E. Bullmore and Sporns, 2009; Cao et al., 2014; Weiss et al., 2011]. The theory of structural controllability in brain networks utilizes the fact that network controllability might be a mechanism of cognitive control. Specific nodes (neurons) at critical locations within this anatomical network can act as drivers, inducing it into specific modes of action (cognitive functions) [Gu et al., 2015].

2.5 STRUCTURAL BALANCE

The dynamics of complex networks is often determined by nature of connections, other than the patterns in connectivity. For example the stability of social networks depends on the positive/negative relations shared by individuals. This was demonstrated by Granovetter to provide interesting insights into strong and weak ties in social networks [Granovetter, 1973]. The variability of edge strengths is also observed in neuronal networks by virtue of dynamic nature of synaptic strengths [Abbott and Nelson, 2000]. Cartwright and Harary have studied dynamics of social networks by considering friendly and antagonistic relationships to explore the frustration in the network (Figure 2.4) [Cartwright and Harary, 1956; Harary, 1953]. These studies form the foundation of an area that focuses on structural balance in the network as an emergent property arising out of cross talks among its elements.

Structural balance connects the local and global properties of the network. The principles underlying the concept of structural balance are based on theories in social psychology dating back to the work of Heider in 1940s [Heider, 1946]. This was generalized and extended to the field of network science in 1950s by Cartwright and Harary [Cartwright and Harary, 1956; Harary, 1953]. Since then the study of structural balance has grown into an important discipline in network science. Research looking at the dynamics of structural balance seeking evolution over time has produced models of social evolution via reassessing person's likes and dislikes [Antal, Krapivsky, and Redner, 2005; Marvel, Strogatz, and Kleinberg, 2009]. Emerging from the analysis

of relationships among individuals, research in political science has shown that during international crises structural balance among nations can provide a good rational for their actions [Moore, 1978]. Based on analysis of plethora of data coming from online social networks, it has been suggested that the dichotomy of trust/distrust in online ratings has similarities with dichotomy in structural balance [Guha, Kumar, Raghavan, and Tomkins, 2004; Kunegis, Lommatzsch, and Bauckhage, 2009].

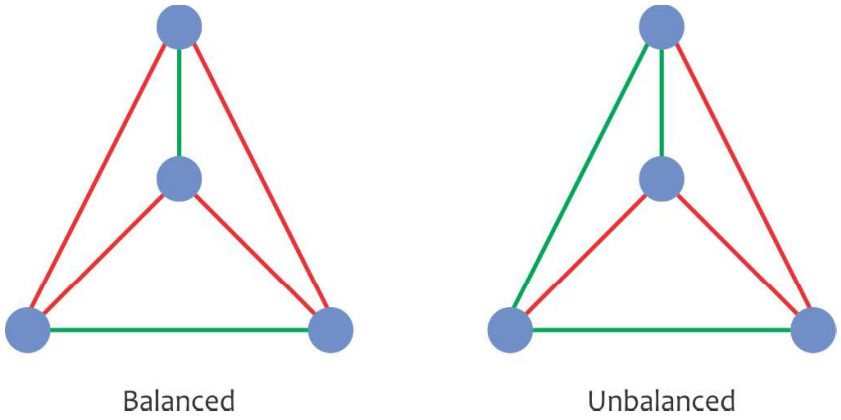

Figure 2.4 : The labelled four node complete graph. Red edges represent animosity and green edges represent positive relationship. Figure adapted from Chapter 5 [Easley and Kleinberg, 2010].

Analogous to the idea of relationships, neurons are known to have cross talk with each other via electrical and chemical synapses. These synapses can be excitatory or inhibitory in nature [Strata and Harvey, 1999]. The synaptic connections are plastic in response to external stimuli. At the same time, internal dynamics also contributes to this plasticity of nervous systems. Hence, we borrowed the concept of structural balance for its application in *C. elegans* neuronal network. Apart from investigating the nature of structural balance in this network, we also developed a metric to quantify the extent of structural balance. Our analysis has led to interesting insights into the nature of excitatory and inhibitory subgraphs of CeNN (Chapter 7).

2.6 BRAIN FUNCTIONAL NETWORKS

Structural connectivity in itself is not sufficient to explain the operations of brain. Complex emergent properties of brain function are not apparent from its wiring diagram alone. This is because wiring alone does not account for the physiology of neuronal interactions responsible for the repertoire of task-dependent neuronal responses. These details can be captured by examining the functional connectivity among remotely located brain areas [K. J. Friston, Frith, Liddle, and Frackowiak, 1993; K J Friston et al., 1994; Karl J. Friston, 1994; Park and Friston, 2013]. Functional connectivity, which records time series along with neuronal activity, can be extracted with various techniques such as cellular recordings, electro encephalon graph, magneto encephalon graph, positron emission tomography, and functional magnetic resonance imaging.

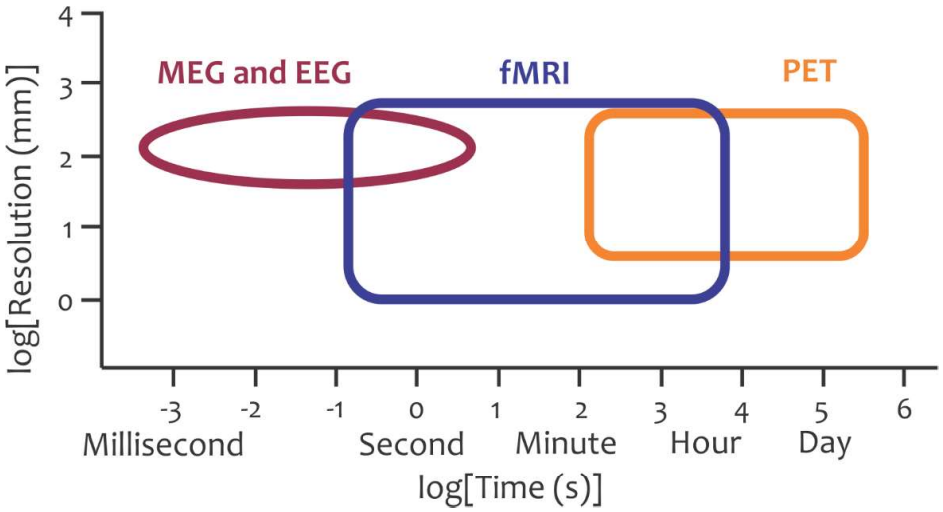

Figure 2.5 : Temporal and spatial resolution of different brain imaging techniques. Figure adapted from [Meyer-Lindenberg, 2010]

Unlike its structural counterpart, functional connectivity is highly time dependent and can change on the scale of hundreds of a millisecond (Figure 2.5). It is also dependent upon the surrounding and task. A balance of spatial and temporal resolution is required to extract the functional connectivity of the brain. Functional magnetic resonance imaging (fMRI) provides such a balanced representation of brain activity. fMRI relies on the assumption that brain functions depend on recruitment and coordinated interaction among different regions. The temporal dynamics causes hemodynamic response functions which in turn has its origin in blood oxygen level dependent changes (BOLD) that are associated with neuronal activity in the brain [Gore, 2003] (Figure 2.6).

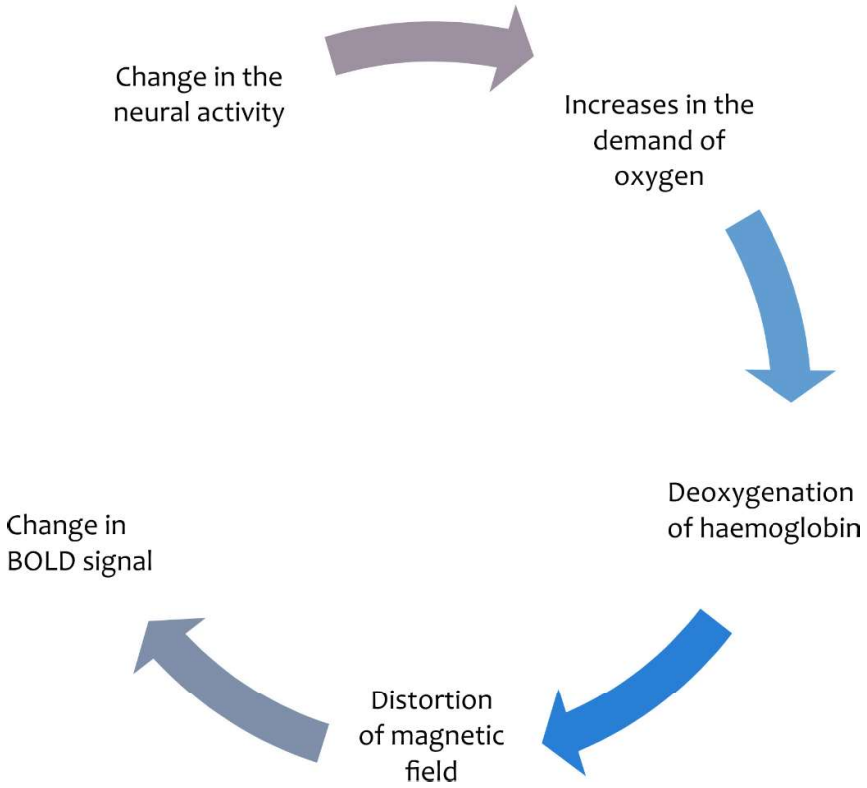

Figure 2.6 : fMRI technique assumes causal connection between 'neural activity' and 'BOLD signal'.

A general framework for capturing deviations from statistical independence involves following steps: Pre-processing, Component extraction, Finding correlations and Creating networks. fMRI signals can be utilized for construction of brain functional networks which can be analysed to extract graph theoretical features which are further exploited for disease diagnosis [E. Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; van den Heuvel and Hulshoff Pol, 2010]. Techniques such as multivariate classification and deep learning can be used in conjunction with functional brain network analysis for clinical diagnosis of neuropathologies such as schizophrenia and Alzheimer's disease [Demirci et al., 2008; Sarraf and Tofighi, 2016; Sundermann, Herr, Schwindt, and Pfleiderer, 2014]. Based on empirical data of functional activity from patients and healthy subjects, we implemented construction and analysis of brain functional networks towards identification of network features useful as markers of schizophrenia (Chapter 8).

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