HUMAN BRAIN ANATOMICAL CONNECTIONS TO GRAPH THEORY

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Abstract

The brain is a complex organ of soft nervous tissue in the skull of vertebrates. It is one of the largest and most complex organs in the body. Information is continuously being processed and transferred between interdependent regions within the brain. The anatomical connection probabilities (ACP) between cortical and subcortical brain gray matter areas are estimated from diffusion-weighted magnetic resonance imaging (DW-MRI) techniques to assess the probability of any given two areas being connected. Those areas are connected by at least a single nerve fiber, which conducts nerve impulses. Current resting-state functional magnetic resonance imaging (fMRI) studies have correlated the inter-regional functional connectivity exhibiting a small-world topology, signifying an arrangement in the brain which is a profound construction of clustered sub-networks. I have collected published data from 15 different cases studies that have examined the sub-network connections to small-world topology. One particular research study examines the clustered sub-networks of the brain by using resting-state data of 28 healthy subjects conducted at the Institute of Clinical and Experimental Neurosciences in Amsterdam. The individual connectivity graphs were developed out of all cortical and sub-cortical voxels with the connections showing inter-voxel functional connectivity. Voxels are a unit of graphic data that characterizes a point in three-dimensional space that relates to a pixel in an image. The components of the nervous system and their interactions are characterized as networks and are mainly represented as graphs where thousands of nodes are interconnected. Graph theory is a mathematical framework that helps put the interconnection of the human brain anatomical network into perspective. This theory provides a viewpoint that helps provide new insights in the discovery of

small-world topology, scale-free networks and the data on anatomical and functional properties of magnetic resonance imaging (MRI) studies using artificial and actual human data. In my recent studies, I investigated diffusion weighted MRI scans of patients that have suffered from either a severe stroke or brain trauma. Using graph theoretical analysis of functional brain networks, I was able to assess the functional connectivity of the brain of the patients, one of the patients being my father. The purpose of this thesis is to examine the connectivity distribution of the number of inter-voxel connections and how a combined small-world and scale-free organization can help identify the functionally connected regions of the human brain.

Introduction

The human brain is one of the most complex systems in nature. Neuroscientists have referred to the brain as the final frontier of science (Pavlopoulos et al., 2011). A substantial amount of the brain's physiological functions involves collecting information from the body, interpreting the information, and directing the body's response. The brain recognizes odors, light, sounds, and pain. The study of anatomical and functional connectivity of the nervous system creates an understanding of the brain specialization and integration (Sporms et al., 2005). Functional connectivity between different brain regions can be inferred from temporal relationships in the neuronal activity, which in turn can be revealed by measuring the coherence of resting-state. Low frequency oscillation during fMRI time series may result from physiological processes such as respiration and cardiac oscillations or may reflect neuronal activation enabled by increased blood flow; the matter is the focus of an on-going debate (Birn et al. 2006; Wise et al., 2004). When you have oscillation, it is characterized by frequency and wavelength. The SI unit used to measure frequency is hertz; one hertz means that a cycle repeats once per second. To define low frequency oscillations as it relates to the subject at hand, low frequency corresponds an electronic signal that is less than 20 hertz which produces a rhythmic pulse. Low frequency oscillations of fMRI are known to aid in functional networks such as the motor, visual, and auditory regions.

A recent human study on resting-state fMRI involving 28 subjects on a 3 Tesla MR scanner showed how an individual dataset can be used to form a functional connectivity graph. In this context, a graph consists of a set of vertices representing the nodes and set of edges representing the connections between the nodes (Pavlopoulos et al., 2011). A graph can show functional brain connections through a network of regions. The brain connections provide direct links to endow one with the ability to systematize information and communicate effectively. There are two classifications of networks that help identify the number of connections per nodes. Small-world networks show short distances between nodes and a high level of clustering in the network; these graphs can be produced using the Watts-Strogatz model (Barabasi and Albert, 1999; Barabasi and Bonabeau, 2003). In contrast, scale-free networks are characterized by the nodes with on average a low number of connections per node with the presence of a small number of highly connected nodes that guaranteeing global connectivity (Barabasi and Albert, 1999; Barabasi and Bonabeau, 2003). The most significant properties that distinguish the topology of intricate networks and indicate whether networks are either small-world or scale-free are a connectivity distribution that follows power-law scaling.

Background Information

Neurophysiology

The nervous system is organized anatomically into two major divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system (PNS), which is composed of all nerves not within the CNS. Neurons are electrically excitable cells that transfer and process information through electrical and chemical signals. Chemical signals pass from one neuron to another at junctions known as a synapses. Visual, auditory, and motor processing is carried out within functional areas of the human brain. Visual, auditory and motor information are projected via parallel pathways to different regions of the brain. The figure 1 below illustrates the movement of information, which determines the reaction time as well.

stimulus → sensory neurons → brain/interneurons → motor neurons → response

Figure 1: The process of the movement of information in the brain.

Certain neurological deficits can affect specific regions of the brain that can preventing visual, auditory and motor information from passing from one neuron to another (Decety et al., 1997). Transient ischemic attacks (TIA), often labeled as a "warning stroke", are caused by a temporary arterial blockage in the brain. The only difference between a TIA and a stroke is that the blockage is temporary in a TIA (American Stroke Association, 2015). However, a stroke occurs when the blood supply is interrupted in a part of the brain, depriving brain tissue of oxygen and nutrients. The brain cells begin to die, leading to functional impairments.

The linkages between stimulus and response as shown in figure 1 can be shown through a series of graphs and/or models from a mathematical theory known as graph theory.

Graph theory

Graph theory concerns the relationships among lines and points. Having at most one line between any two points and not having a line coming back to the original vertex is a description of a simple graph as shown in the figure 2 below.

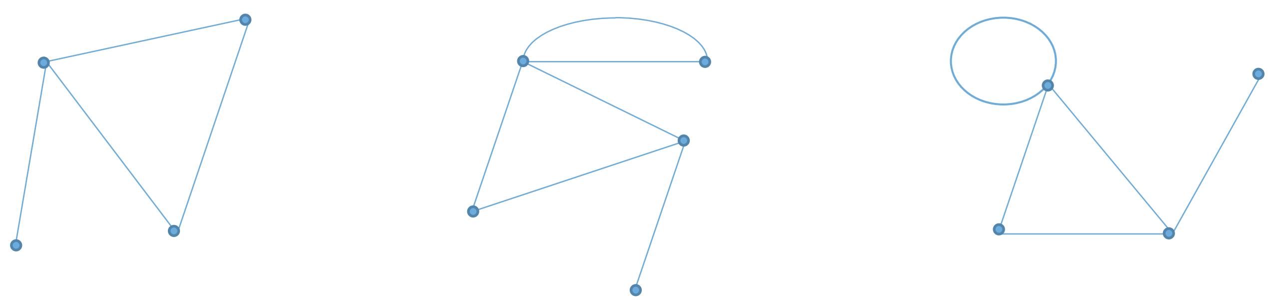

Figure 2: Graphs can be defined based on the nature of connections, or edges, between points, or vertices. On the left to right side, a simple graph, nonsimple graph with multiple edges, and a nonsimple graph with loops

The brain is a complex network which, if depicted as a graph, would consists of multiple edges (lines) and vertices (points). Within the fields of science and medicine, network analysis can be applied to determine effective strategies for treating diseases and also enable early diagnosis of disorders (Cheng, S., 2015). Clustering coefficient, scale-free and small-world, degree distribution, Watts and Strogatz, and Barabasi-Albert models are some of the highlighted terms in graph theory; these models and methods can help to better understand the biological significance of functional connectivity in the human brain (Mathias and Gopal, 2001).

Materials and methods

Connecting MRI data with graph theory

Magnetic resonance techniques are used to produce views of the human body for diagnostic purposes. The resulting image is based upon different tissue parameters such as proton density, T1 relaxation time and T2 relaxation time (Iturria-Medina et al., 2007). There are three broad tissue regions evident in an MRI; these are gray matter, white matter, and cerebro-spinal fluid. Gray matter consists of neuronal cell bodies, neuropil, glial cells, and capillaries. The cerebral cortex is a noteworthy example of gray matter, but gray matter is distributed in other regions as well, regions involved in muscle control, visual and sensory perception (Iturria-Medina et al., 2007). White matter connects gray matter regions to each other and carries impulses between neurons. MRI techniques can be combined with graph theory to summarize connection patterns among the gray matter areas of the brain using three major steps. Certain algorithm and probabilities that help assess these connection patterns. The first step of the procedure is solving the cerebral volume, using a brain graph expressed as $G_{\text{brain},0} = [N_0, A_0, W_0]$,which is a representation of the set of nodes belonging to some of cerebral tissue (N_0), the set of white matter links (A_0) between nodes in N_0 , and a set of real numbers representing arc weights (W_0) (Iturria-Medina et al., 2007). This graph is used to ensure that only certain pairs of nodes with high probability of gray/white matter are shown. The second step uses an algorithm to solve the most probable path trajectory between any two nodes. The last step of the procedure is redefining the previous brain graph showing the initial nodes set into the non-overlapped gray matter and clustering the remaining nodes $G_{\text{brain}} = [N, A, W]$. N represents the nodes of the gray matter areas and A as the direct white matter connections between gray matter regions. Lastly, W is the probability of connections between the gray matter areas. Figure 3 illustrates a dissected brain showing gray and white matter regions.

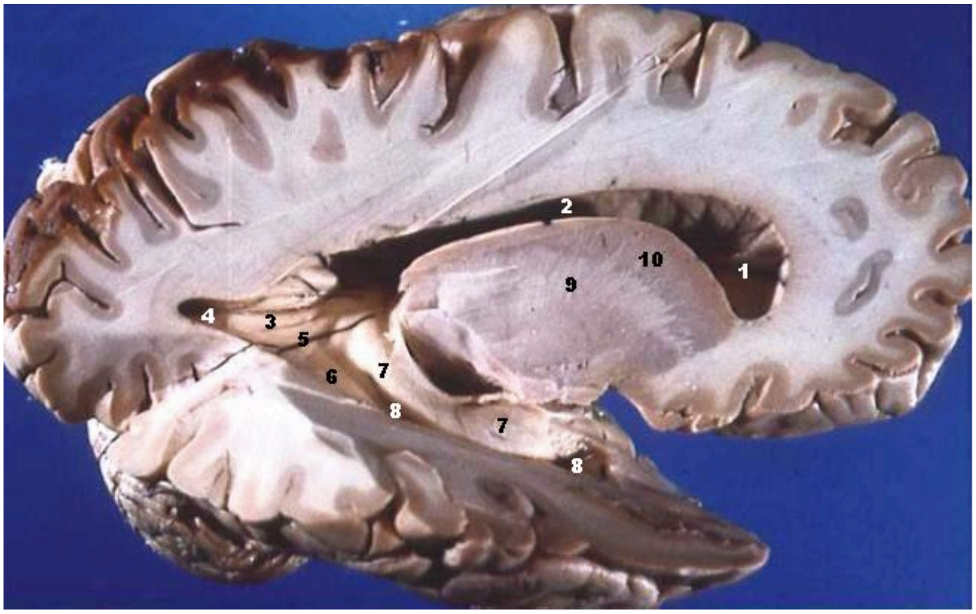

Figure 3: Human brain dissected lateral view showing gray matter and white matter. The numbers indicate the different portions of the brain such as the frontal, parietal, occipital, temporal lobe (adapted from Department of Cellular Biology & Anatomy, Louisiana State University Health Sciences Center Shreveport).

Three connectivity measurements

Connections between regions are measured by anatomical connection strength (ACS), anatomical connection density (ACD), and anatomical connection probability (ACP). ACD, ACS, and ACP are three different measures used for computing connections between any gray matter subgroups. ACD evaluates if a pair of zones has diverse or equivalent amounts of connection density relative to another pair of zones with a different number of nodes (Iturria-Medina et al., 2008). ACS estimates the information flow between any two regions. The fiber connector volume on the surface of the two areas is assessed by checking the quantity of hubs on the surfaces of the zones included in the connection, where every hub is joined by the most extreme likelihood. ACP measures the most extreme likelihood of any two regions being joined at any rate by one nervous fiber connection and is evaluated as the highest connectivity quality between the shallow hubs of both included zones. The gray matter regions can be related independent of the quality and density of their conceivable connections. Utilizing the ACP measure for zone-zone connections for potential gray matter has led to artificial and human trials, which is a desirable outcome because in the past connectivity information was limited and only available using human pathological specimens and invasive studies (Iturria-Medina et al., 2008).

Small-world and clustering coefficient

The term small-world network, according to Watts and Strogatz, are networks "highly clustered (C), like regular lattices, yet have small characteristic path lengths (L), like random graphs" (Watts and Strogatz, 1998). Small-world networks correlate to the average shortest path length and clustering coefficient concepts. Path lengths is a measure of the distance between nodes in the network. Path length is defined as the mean of the shortest geodesic lengths (d_{ij}) over all possible pairs of nodes (i and j) (Watts and Strogatz, 1998; Telesford et al.,2011). Small values of L guarantee that data or assets effortlessly spread throughout the network.

$$L = \frac{1}{N(N-1)} \sum_{\substack{i,j=1 \\ i \neq j}}^{N} d_{ij}$$

(1)

The probability of an analyzed connection, $l_{ij} = \frac{1}{w_{ij}}$, defines the probability of nervous fiber connection. The probability depends on the “diffusion data coherence” and the white and gray matter presence along the estimated connection paths (Boccaletti et al., 2006). The optic radiation is a visual pathway that consists of axons from relay neurons in the lateral geniculate body of the thalamus which conveys information to the visual cortex (Decety et al., 1997). The superior longitudinal fasciculus is composed of a bundle of long fibers in the lateral portion of the brain connecting the frontal, occipital, and temporal lobes (Cheng, S., 2015). The long and short range connections supported by the optic radiation and the superior longitudinal fasciculus can have comparable arc length values relying upon the connection probabilities. However, the clustering coefficient is the measurement that demonstrates the tendency of a graph to be divided into clusters of strictly connected neighborhoods (Watts and Strogatz, 1998). The average clustering coefficient of the whole network C_{average} is given below

$$C_{\text{average}} = \frac{1}{N}\sum_{i=1}^{N}\frac{E_i}{k_i(k_i-1)}$$

(2)

The closer the coefficient is to 1, the more likely the network will form clusters. A cluster is referred to as a community, a group of nodes having denser relations with one another than with the rest of the network (Fortunato, S., 2010). Overall, a short path length shows that nodes of the same sub-network and diverse sub-networks are connected by short paths (Watts and Strogatz, 1998), suggesting a high level of global and local communication efficiency. In figure 3 below you can see the difference between random, regular, and small-world networks and how the numbers of connections are broken and rewired to make long distance connections at random locations.

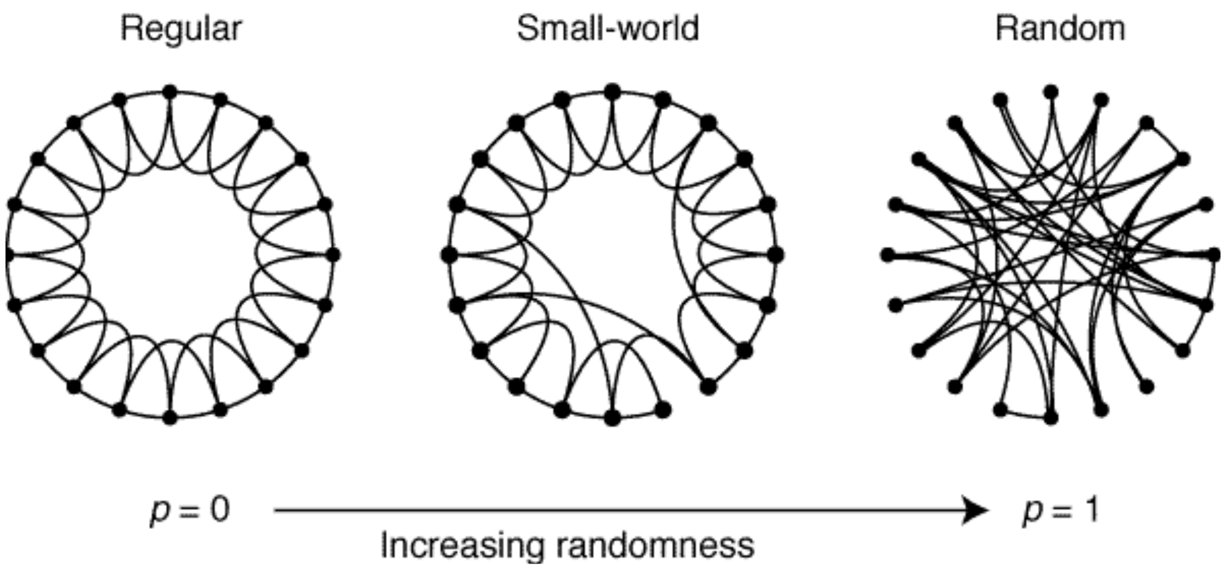

Figure 4: Regular network: all cells are only coupled to their nearest neighbors. Small-world is the small numbers of connections are broken and rewired to make long distance connections at random locations Random network are the longer distance connections, and the network loses the property that most connections are local.

Degree distribution/ scale-free

Not all complex networks have the same degree; which is the number of edges to the vertex. One of the most prominent characteristics is degree distribution $P(k)$. Degree distribution properties are regularly used to characterize a network into distinctive categories. For a power law distribution $P(k) \sim k^{-\gamma}$, the degree distribution is

$P(k) \sim k^{-\gamma-1}$ form and describes the probability of a random chosen node in the network to have a degree greater than k arc (Lima-Mendez et al., 2009). A network that exhibits a power law distribution is known as a scale-free network. Scale-free networks are distinguished by a degree distribution that decreases as a power law with degree exponents (α) varying in range $2 < \alpha < 3$. Scale-free is constructed by dynamically adding nodes to an existing network and introducing links to existing nodes with attachments so that the likelihood of connecting to a given node (i) corresponds to the quantity of existing connections k_i that node has (Mason, 2011). The cumulative degree distribution $P_c(k)$ is utilized to diminish the impacts of noise relating to small networks (Strongatz, 2001). The duration of all experiments exceeded 30 days, and the reported values shown in the results are based on investigator-reported measurements from documented literature data.

Results and Discussion

Institute of Clinical and Experimental Neurosciences in Amsterdam

Anatomical brain connectivity between gray matter structures were reported recently in human studies conducted at the Institute of Clinical and Experimental Neurosciences in Amsterdam (Cordes et al., 2001; Wise et al., 2004). The authors studied MRI scans of 28 healthy subjects, and assumed that two regions were connected if the regions showed significant correlations in the cortical thickness. Significant correlations were obtained between 0.65 and 0.88 *p* values range. Small-world networks show a high-level of local ordering, showing the development of sub-graphs, yet with an average short path length of around the same length as the path length of random organized networks, guaranteeing an ideal level of global connectivity (Latora and Marchiori, 2001). The recorded data from the resting-state group indicated that the average small-world index sigma for the threshold differs between 0 and 0.7 and the distribution in the graph varies between 4000 and 20(Van den Heuvel et al., 2008). This sigma increase suggests a small-world organization of the graph. The results of the averaged clustering coefficient indicated a higher level of ordering in the resting-state functional graph in comparison to a random connected graph. The group data did not show any outliers. There was a higher level of ordering in the resting-state functional graph in comparison to a random connected graph. The random connected graphs with a corresponding connectivity degree and distribution. As the threshold increases, more paths are removed. When more paths are removed, this removal has an effect on the voxel distance (Van den Heuvel et al., 2008). The short path length shows a proficient correspondence exchange between regions that frame such resting-state networks and in addition a constant information transfer between regions of different networks.

Conclusion

This thesis shows possible small-world and scale-free organization of the human brain at a voxel level, and it helps improve understanding between the neuronal correlate of resting-state functional connectivity. Resting-state functional brain data of 28 subjects was collected as a part of a research project that explained and demonstrated how a network was constructed out of all cortical and subcortical voxels with connections between linked voxels. Using graph theory to interpret the data collected in that project, I conclude that the clustering coefficient was higher than that of a random graph, implying small-world organization of the human brain during resting state. Also the connectivity distribution followed a power-law distribution for a range of fixed threshold and connectivity degrees. These results demonstrated a scale-free topography of the human brain. The importance of a scale-free topology is that it guarantees efficient and powerful transport and flow processing in the network by avoiding congestion of information flow (Barabasi et al., 1999). Small-world and scale-free, consolidated together guarantee an ideal form of network organization, forming a balance between maximum communication efficiency and minimum wiring (Mathias and Gopal, 2001). My interpretation of the results collected by the Institute of Neuroscience in the Netherlands, is that large cerebrum regions are overall joined with around the same number of other brain regions, while sub-regions have on average a lower number of connections. At the same time, they stay comprehensively connected through a method of a small number of connected hub-regions. Stroke and other neurological diseases regularly influence the entire brain framework and henceforth a network approach is liable to be more qualified to research the pathophysiology fundamental neurological deficits in the unhealthy cerebrum than the common functional MRI studies. In the future, I would like to collect additional data and advance the analysis of the correlation between the white and gray matter regions in the brain using graph theory. By showing the voxel scale in the brain, we are then provided an insight into neurological diseases such as schizophrenia, Alzheimer's, and Parkinson's disease. The brain is a complex system and information is continuously being processed. We have barely scratched the surface of understanding the complex functions of the brain.

Appendix:

Distance: The distance between two arbitrary vertices i and j in a graph G is the length of a shortest path from i and j in graph G. If no such path exists, then we assume that the nodes are not connected.

Clustering coefficient: A graph parameter that measures the tendency of a graph to be divided into clusters. A cluster is a subset of vertices that contains a large number of edges connecting these vertices to each other. N is the number of vertices (that is, if $G = (V, E)$ then N is the number of elements in V), the local clustering coefficient is:

$$C_{\text{average}} = \frac{1}{N}\sum_{i=1}^{N}\frac{E_i}{k_i(k_i - 1)}$$

The closer the local clustering coefficient is to 1, the more likely it is for the network to form clusters.

Scale-free: Nodes representing bio entities and edges modeling the interaction between them. This real world network is constructed by adding nodes to an existing network and introducing links to existing nodes with preferential attachment so that the probability of linking to a given node i is proportional to the number of existing links k_i that node has.

Power-law distribution: k is the number of links originating from a given node and *P(k)* the probability that the degree of a randomly chosen vertex equals k. $P(k){\sim}k^{-\gamma}$, where γ denotes the degree exponent.

Watts and Strogatz model: This model is used to describe networks that follow the small world topology.

Barabasi-Albert model: This model describes scale-free networks and it is one of the most basic models since it describes most of the biological networks.

(Further descriptions on these particular terms can be found on www.ncbi.nlm.nih.gov/pmc/articles/PMNC3101653/)

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