Identifying Diurnal Variability of Brain Connectivity Patterns using Graph Theory

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IDENTIFYING DIURNAL VARIABILITY OF BRAIN CONNECTIVITY PATTERNS USING
GRAPH THEORY

by

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ABSTRACT

Circadian rhythms are 24-hour fluctuations determining periodicity in a wide range of physiological processes, including neural activity and hormone secretion, which controls sleeping and feeding habits. Despite significant diurnal variation in human brain function, neuroscientists have rarely considered the effects of time-of-day on their studies. Moreover, there are interpersonal discrepancies in sleep-wake patterns, diurnal preferences, and daytime alertness (known as chronotypes), which can cause different diurnal profiles in human cognition and brain performance. The study of circadian typology differences has increased in recent years, however, examining the effects of both time-of-day and people’s chronotype requires further elucidation. In the present study, we performed graph-theory based network analysis on resting-state functional MRI (rs-fMRI) to explore the topological differences in whole-brain functional networks between the morning and evening sessions, as well as between extreme morning-type and evening-type participants. To that end, 62 individuals (31 extreme morning- versus 31 evening-type) underwent two fMRI sessions: about 1 hour after the wake-up time (morning) and about 10 hours after the wake-up time (evening), scheduled in accord with their declared habitual sleep-wake pattern on a regular working day. The findings of this study revealed the effect of time-of-day on the functional connectivity patterns, and there was no significant difference in chronotype categories. Compared to the morning session, we found relatively higher network segregation (i.e., higher small-worldness and modularity) and higher synchronization in the evening session. Interestingly, local graph measures were altered predominantly across the left hemisphere in areas involved in language processing, sensorimotor control, as well as subcortical portions of the limbic system.
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CHAPTER 1: INTRODUCTION

Human Brain Connectivity

The human brain comprises approximately 86 billion neurons connected through approximately 150 trillion synapses that allow neurons to transmit electrical or chemical signals to other neurons (Azevedo et al., 2009; Pakkenberg et al., 2003). Studies on modeling the human brain as a complex system have grown remarkably as neuroscientists seek to understand the comprehensive information underlying cognition, behavior, and perception (Bassett and Bullmore, 2006; Bullmore and Sporns, 2009, 2012; Craddock et al., 2013; Friston, 2011; He and Evans, 2010; Park and Friston, 2013; Reijneveld et al., 2007). Exploring the human brain from the viewpoint of connectivity patterns reveals important information regarding the structural, functional and causal organization of the brain. Among the connectivity techniques, functional and effective connectivity have been the focus of the computational studies in recent years (Farahani and Karwowski, 2018; Friston, 1994, 2011). Functional connectivity refers to the temporal correlations among spatially remote neurophysiological events, whereas effective connectivity refers to the causal interactions between neuronal units of the brain network (Friston, 1994). Further, the human connectome (i.e., mapping the connectivity patterns of the human brain) has become an increasing topic of interest in the area of human neuroscience and can be studied using network science and graph theory (Kelly et al., 2012; Sporns, 2013a; Sporns et al., 2005; Van Essen et al., 2012).

Diurnal (Circadian) Rhythm

Circadian rhythms are natural, internal 24-hour fluctuations in most living organisms, regulating a variety of physiological functions, including the sleep-wake patterns (Borbély, 1982; Dijk and
Lockley, 2002; Schmidt et al., 2012), body temperature (Refinetti and Menaker, 1992), endocrine and metabolic rhythms (Hastings et al., 2007), gene expression (Storch et al., 2002), musculoskeletal activity (Aoyama and Shibata, 2017), as well as a wide range of brain functions and cognitive tasks (Schmidt et al., 2007). Studies on human cognitive tasks have shown circadian variations in attention (Valdez et al., 2005), working memory (Ramírez et al., 2006), motor (Edwards et al., 2007) and visual detection (Tassi et al., 2000). It should be noted that in studies on the brain function, multiple scales of brain organization from that of individual cells and synapses (Gilestro et al., 2009; Kuhn et al., 2016; Vyazovskiy et al., 2008) to brain regions and large-scale functional connectivity (Blautzik et al., 2013; Hodkinson et al., 2014; Shannon et al., 2013; Steel et al., 2019) have been considered.

A chronotype is a biologically driven circadian typology that generally refers to the individual differences in sleep-wake cycles, diurnal preferences, and alertness throughout the day (Roenneberg et al., 2003; Susman et al., 2007). Traditionally, individuals fall into morning-type (“early larks”) or evening-type (“night owls”) categories. Evening chronotypes typically have phases of behavioral and physiological circadian clocks shifted toward later hours than morning chronotypes (Bailey and Heitkemper, 2001; Kerkhof and Van Dongen, 1996). Various studies have shown that people’s chronotype discrepancies have resulted in significantly different diurnal profiles in human cognition and behavior (Horne et al., 1980; Norbury, 2020; Schmidt et al., 2007; Valdez et al., 2012). Circadian variations in performance-related neural activity were also reported in studies utilizing chronotype-based paradigms (e.g., Fafrowicz et al., 2009; Gorfine et al., 2007; Peres et al., 2011; Schmidt et al., 2009, 2012, 2015; Vandewalle et al., 2009, 2011). Interestingly, Facer-Childs et al. (2019) observed that the primary differences between early and late circadian phenotypes were located in the default mode network (DMN).

However, there is limited functional MRI (fMRI) studies investigating the impact of time-of-day and chronotype on their results. Potentially, most studies assume that diurnal fluctuations of brain
connectivity patterns as well as human chronotypes are relatively insignificant and are unlikely to lead to a substantial systematic bias into group analysis. Furthermore, previous resting-state fMRI studies that have focused on circadian rhythms have yielded contradictory or sometimes even ambiguous findings (Blautzik et al., 2013; Cordani et al., 2018; Hodkinson et al., 2014; Jiang et al., 2016; Shannon et al., 2013; Steel et al., 2019), perhaps because of varying analysis pipelines. There are also inconsistencies in diurnal fluctuations of brain activation patterns in task-based fMRI studies (Gorfine and Zisapel, 2009; Marek et al., 2010).

Graph Theoretical Analysis of the Brain

The human brain is one of the most complex networks in the world, and studies on its static and dynamic properties have undergone explosive growth in recent years (Bullmore and Sporns, 2012; Kriegeskorte and Douglas, 2018; Sporns, 2013b). The advances in graph theory and network neuroscience (i.e., the study of the structure or function of the nervous system) offer an opportunity to understand the details of this complex phenomenon and its modeling (Sporns, 2018; Vecchio et al., 2017). Graph theoretical approaches have set up a mathematical framework to model the pairwise communications between elements of a network. In human neuroscience, graph theory is generally applied to either functional or effective connectivity. However, most studies have been devoted to functional connectivity (Bullmore and Sporns, 2009; Goldenberg and Galván, 2015).

Graph-based network analysis reveals meaningful information about the topological architecture of human brain networks, such as small-worldness, modular organization and highly connected or centralized hubs (Bullmore and Sporns, 2009, 2012; Bullmore and Bassett, 2011; He and Evans, 2010; Meunier et al., 2010; van den Heuvel and Sporns, 2013). Small-worldness is a property of some networks in which most nodes are not neighbors of each other but can be reached from every other node by a small number of steps. This characteristic is well suited to the study of
complex brain dynamics, and it confirms efficient information segregation and integration in the human brain networks with low energy and wiring costs (Watts and Strogatz, 1998). Recent studies demonstrate that the small-world property of brain networks experiences topological alterations under different cognitive loads and during development (Bassett et al., 2011; Braun et al., 2015; Cao et al., 2016; Liang et al., 2016), as well as in neurological and mental disorders (Abós et al., 2017; Dai and He, 2014; Filippi et al., 2013; Fleischer et al., 2019; Fornito and Bullmore, 2015; Fornito et al., 2012b; Gong and He, 2015; Hojjati et al., 2017; Jalili, 2017; Ashtiani et al., 2018; Stam, 2014; Xia and He, 2011). These alterations may provide novel insights into the biological mechanisms underlying human cognition, as well as health and disease.

Research Objectives

The primary objective of this study is to investigate alterations of neural activity in different times of the day and detect circadian fluctuations of brain functional networks using resting-state fMRI (rs-fMRI). To this end, we are looking to apply graph-theoretic framework to extract the global and local changes in brain network topology and determine the most informative brain regions that are substantially different during the course of a day. Moreover, we will consider the participants’ chronotype (i.e., a person’s natural inclination with regard to the times of day when they prefer to sleep or when they are most alert or energetic), which could have affect the results. The main objective is divided into following segments.

Objective 1: To study whether time-of-day (morning and evening session), has an effect on the topological properties of the brain topology.

Objective 2: To investigate the possible topological changes between morning-type and evening-type participants in different brain regions.
Objective 3: To investigate whether global and local measures are correlated with the cognitive variables derived from the assessments and questionnaires (e.g., ME scale, AM scale, ESS, or any other cognitive/behavioral variables) across participants.
CHAPTER 2: LITERATURE REVIEW

The main content of this chapter is adapted from the systematic review paper by Farahani et al. (2019b) which has been published in the *Frontiers in Neuroscience*\(^1\) journal.

Brain connectivity investigations using fMRI time-series were initiated in the mid-1990s and provided a new tool for researchers, especially neuroscientists, to study the human brain network with high precision.

Existing Methods for Modeling the Connectivity Patterns (using fMRI)

Computational methods available for brain connectivity are divided into two general categories: functional connectivity and effective connectivity (Friston, 1994, 2011). Briefly, functional connectivity provides information about the statistical dependencies or temporal correlations between spatially remote neurophysiological events, whereas effective connectivity is concerned with the directed influence of brain regions on each other (Friston, 2011). In the following, we will review the computational methods that are presented in the literature for investigating both types of connectivity with a greater focus on graph theoretical approaches in separate sections (Figure 2.1).

Functional Connectivity

Functional connectivity refers to the temporal correlations between BOLD signals from spatially remote brain regions (Friston et al., 1993; Lee et al., 2003). Functional connectivity methods in fMRI studies are broadly divided into model-based (e.g., cross-correlation, coherence analysis, and

\(^1\)https://www.frontiersin.org/articles/10.3389/fnins.2019.00585/full
Figure 2.1: Taxonomy of existing methods for modeling functional and effective connectivity patterns using fMRI. Each of the identified methods can be represented in terms of a graph, where the nodes correspond to cortical or subcortical regions and the edges represent (directed or undirected) connections (Bullmore and Sporns, 2012); thereby all of them can be further examined with graph-theoretic measures.

statistical parametric mapping) and model-free (e.g., decomposition-based analysis, clustering, and mutual information) groups.
Model-based Methods

Model-based methods typically identify brain connectivity networks by selecting one or more “seed” regions and then determining whether there is a linear link between seed regions and other regions using predefined criteria (Li et al., 2009a). Despite their widespread use and simple interpretation in identifying functional connectivity, the requirement for prior knowledge (particularly in rs-fMRI), dependency on the seed selection, and the inability to detect non-linear forms of interaction, restrict the discovery of all plausible functional architectures (Farahani and Karwowski, 2018; Farahani et al., 2019b).

Cross-correlation and coherence: Cross-correlation analysis is the most traditional method for testing functional connectivity, which is defined by measuring the correlation between the BOLD signals of any two brain regions (Cao et al., 1999). The computational complexity of this method is extremely high when calculating the correlation of two series at all lags (Cecchi et al., 2007). Fortunately, a large number of fMRI studies have overcome this drawback by computing only the correlation with zero lag due to the short duration of the hemodynamic response of blood (Friston et al., 1994b; Saad et al., 2001). Moreover, correlations are sensitive to the shape of the hemodynamic response function (HRF), which causes variations across different individuals and different brain areas (Lee et al., 2001; Miezin et al., 2000). Furthermore, a high correlation may be observed among regions that practically have no blood flow fluctuations. Uncontrolled physiological noise in the brain (e.g., from cardiac and respiratory variations) can also result in high correlations between brain regions (Friston et al., 1994a). To address these problems, Sun et al. (2004) suggested a new measure, termed coherence, which is the spectral representation of correlation in the frequency domain.

Statistical parametric mapping (SPM): SPM is another model-based approach used to detect region-specific effects (e.g., brain activation patterns) in neuroimaging data, such as fMRI and PET,
using a combination of the general linear model (GLM) and Gaussian random field (GRF) (Friston et al., 1991). The GLM helps estimate the parameters describing the spatially continuous data by performing a univariate test statistic on each voxel. GRF theory is applied to address the multiple comparisons problem for continuous data (i.e., images) when making statistical inferences over a volume of the brain, an approach similar to the Bonferroni correction for the analysis of discrete data (Worsley et al., 1992).

**Model-free Methods**

In contrast to seeds-based methods, model-free methods need no seeds selection. Also, model-free methods may be beneficial in studies where there are no temporal or spatial patterns, as well as in quantifying non-linear neuronal interactions (Farahani et al., 2019b).

**Decomposition-based analysis:** PCA can express the fMRI data with a linear combination of orthogonal contributors that have the greatest impact on the data variance. Each contributor contains a pattern of time variability (or a principal component) multiplied by a pattern of spatial variability (or an eigen map). The created eigen maps reflect the connectivity architecture of the brain (Baumgartner et al., 2000; Worsley et al., 2005). Despite the ability to explore the whole-brain connectivity, PCA fails to detect activations when the contrast-to-noise ratio is low (Baumgartner et al., 2000). Also, how to select the optimal number of components has become an open question. Thus, PCA commonly serves as a preprocessing step in fMRI studies through dimension reduction (Li et al., 2009a). Another decomposition-based method, called independent component analysis (ICA), attracted the attention of researchers in rs-fMRI studies. The major difference between ICA and PCA is that the components in ICA should be as independent as possible (Comon, 1994; Hyvärinen and Oja, 2000). Note that a violation of component independence would reduce the efficiency of ICA (Calhoun et al., 2001). Furthermore, finding the optimal number of independent
components is controversial because choosing a small number of components can have a significant effect on ICA results (Ma et al., 2007), particularly when used for decoding purposes (Douglas et al., 2011, 2013). Finally, ICA cannot discriminate between signals of interest and signals of no interest (e.g., physiological noise, unexplained signal variations), leading to overfitting and invalid assessment of statistical significance. To address this pitfall, Beckmann and Smith (2004) proposed a probabilistic ICA that allows for non-square mixing when there is Gaussian noise.

**Clustering:** The primary goal of clustering algorithms is to group voxels or regions of interest into different clusters based on the similarity between their BOLD time courses (Golay et al., 1998). Hierarchical clustering, $k$-means, fuzzy clustering (fuzzy $c$-means), self-organizing maps, graph-based, and bootstrap analysis are the most well-known algorithms used in fMRI studies (Bellec et al., 2010; Chuang et al., 1999; Cordes et al., 2002; Golland et al., 2008; Lee et al., 2012; Ngan and Hu, 1999; Van Den Heuvel et al., 2008). Among these methods, the largest volume of studies utilizes hierarchical and fuzzy clustering. Hierarchical clustering seeks to construct a hierarchy of clusters based on an agglomerative or divisive strategy (Rokach and Maimon, 2005). Although this method exhibits good efficacy in the presence of respiratory or cardiac noise, its high computational complexity is a serious limitation when examining the whole brain connectivity (Cordes et al., 2002). Fuzzy $c$-means (FCM) is a method in which each data point has a membership value to each cluster, rather than entirely belonging to one cluster as $k$-means. This algorithm performs optimization by updating memberships and cluster centers until convergence (Lahijanian et al., 2016; Lee et al., 2012). It’s worth noting that, given the non-Euclidean nature of MRI data, the use of Euclidean distance in FCM-based algorithms may lead to an invalid result (Farahani et al., 2015, 2018). Van Den Heuvel and Pol (2010) compared the results of clustering algorithms to those of decomposition-based methods and reported a high level of overlap. Future studies may, therefore, pay more attention to these algorithms and, by eliminating the above issues, achieve more acceptable performance in human neuroscience.
Mutual information (MI): MI is an information theoretic concept that quantifies the shared information (undirected) between two random variables (Grassberger et al., 1991; Kraskov et al., 2004). Equivalently, the MI is a model-free technique that does not require any a priori assumptions about the connectivity patterns among variables, thus, it can be applied to detect both linear and nonlinear correlations (Wilmer et al., 2012). Tsai et al. (1999) were among the first to present a theoretical framework for using MI to calculate the fMRI activation map. To further explore the strengths and pitfalls of this method in comparison to other functional connectivity measures, refer to (Bastos and Schoffelen, 2016; Wang et al., 2014a).

Effective Connectivity

The primary goal of effective connectivity analysis is to assess causal interactions between neuronal units of the brain network (Friston, 1994). Studies in this area help researchers better understand the mechanisms underlying neuronal dynamics (Farahani et al., 2019b; Wu et al., 2014). In the following, we review the existing effective connectivity methods with their pros and cons in greater detail.

Model-based Methods

Granger causality (Granger, 1969) is the most traditional model-based method for directional interactions that can be easily implemented. However, Granger causality appears to encounter difficulties when applied to fMRI data due to the underlying assumptions in its modeling (Dang et al., 2017; Wen et al., 2013). Two other model-based methods for analyzing effective connectivity are dynamic causal modeling (Friston et al., 2003) and structural equations modeling (McIntosh and Gonzalez-Lima, 1994). Despite the coherent interpretations provided by these methods, they are highly dependent on prior knowledge, so their application in analysis of rs-fMRI data is limited
The core idea behind GC is that $X$ “Granger-causes” $Y$ if $Y$ can be better predicted using the histories of both $X$ and $Y$ than the past of $Y$ alone (Granger, 1969). Accordingly, past data from one brain region can help estimate the current state in another region. Due to the time mismatch between sampling interval and neural events, the causality method cannot be applied directly to the fMRI signals because it leads to the prediction of causal relationships in BOLD signals rather than neuronal responses (Smith et al., 2012, 2011). To tackle this issue, GC analysis is typically performed by fitting a linear vector autoregressive (VAR) to the time series (Friston et al., 2013; Seth et al., 2015; Seth, 2010). However, linear methods are not suitable for testing GC in higher moments (e.g., the variance). Nonlinear and nonparametric models are used to solve this problem (Dhamala et al., 2008; Roebroeck et al., 2011). Wen et al. (2013) pointed out that several factors may hamper the neural interpretability of GC, such as low sampling rates (Lin et al., 2014), latency mismatches in HRF across distinct brain regions, and the presence of noise. Their findings reflect that GC is a viable method for analyzing fMRI signals when associated confounds are controlled.

**Dynamic causal modeling (DCM):** DCM is based on a general bilinear state equation that quantifies how variations in neural activity in one node are affected by the activation in another node under predefined stimuli (Friston et al., 2003; Stephan et al., 2010). This equation involves a variety of information including the coupling between brain regions, changes in the coupling strength as a result of experimental conditions, and the direct effects on a region (Friston, 2009). DCM provides a powerful statistical platform that estimates the experimental modulation of both intrinsic and extrinsic connections in the brain, and the Bayesian model comparison is executed to choose the best-fitted model (Goldenberg and Galván, 2015). Perhaps the biggest disadvantage of DCM is that it is not exploratory and requires prior knowledge about the hypotheses and model specification to be implemented. However, a recent trend has emerged for comparing numerous models in a more
exploratory manner using a post-hoc analysis, wherein only the largest model is inverted while all of the reduced models would be searched quickly (Friston et al., 2011). Friston et al. (2013) pointed out that GC and DCM play complementary roles in analyzing the causal interactions. In fact, GC can be used generically to any specified time series to identify the coupling between neuronal units, making helpful insights into the dynamic behavior of the human brain in different situations. One might then continue effective connectivity analyses in a hypothesis-driven manner to obtain a further interpretation of the neuronal interactions using DCM (Daunizeau et al., 2011). Notably, although both build upon model selection, they have a fundamental difference. Model selection in DCM is based on a direct comparison between all models (Penny, 2012), whereas in GC this involves testing for the presence of GC followed by selecting the VAR model order using Akaike or Bayesian information criteria (Bressler and Seth, 2011).

**Model-free Methods**

Past efforts to detect effective connectivity mostly relied on model-based methods such as GC or DCM. Model-free methods including probabilistic Bayesian networks, Markov models, and transfer entropy have been developed to determine non-linear forms of directed interactions. These methods do not require a priori assumptions on connectivity patterns due to their exploratory nature (Ramsey et al., 2010), but lagged interactions between fMRI time-courses may be a common shortcoming for most of them (Dang et al., 2017).

**Bayesian network (BN):** BN is a probabilistic model well suited for representing the conditional dependencies over a set of random variables through a directed acyclic graph (DAG; Friedman et al., 1997). Each edge indicates a dependency between two variables (nodes), where the lack of connection between any pair of nodes reflects conditional independence. Each node has a probability distribution: In root nodes, this is prior probability, while in child nodes this is the conditional
probability (Daly et al., 2011; Das, 2004). Gaussian BN (Li et al., 2009b) and discrete dynamic BN (DBN; Rajapakse and Zhou, 2007; Zeng and Ji, 2010) are the most commonly used techniques in this area. Due to the static nature of Gaussian BNs, they are unable to explicitly model the temporal interactions between multiple processes in different parts of the brain (Rajapakse and Zhou, 2007). Compared with Gaussian BN, discrete DBN is not limited by linear assumptions, and it can model temporal processes via a first-order Markov chain (Rajapakse and Zhou, 2007). However, the presence of multinominal distribution in the nodes of discrete DBN causes discretization of the data, leading to a huge loss of information. To overcome the primary limitations of both methods, Wu et al. (2014) proposed a method called Gaussian DBN based on a first-order linear dynamic system.

**Transfer entropy (TE):** TE is a non-parametric approach measuring the transfer of information between joint processes based on information theory (Schreiber, 2000). Because of its non-linear nature, this method is able to properly detect directional connectivity even if there is a wide distribution of interaction delays between the two fMRI signals (Sharaev et al., 2016; Vicente et al., 2011). Although TE and GC are relatively equivalent for Gaussian variables (Barnett et al., 2009), TE needs much less computational time than GC for high model orders and greater numbers of nodes. In addition, TE does not assume any particular model as underlying the interactions, therefore, its sensitivity to all order correlations becomes a privilege for exploratory analyzes over GC or other model-based methods (Montalto et al., 2014; Vicente et al., 2011). However, contrary to the model-based methods, it is more difficult to interpret this measure in functional connectivity analysis due to its generality (Bastos and Schoffelen, 2016).
The first application of graph theory and network analysis can be traced back to 1741 when Leonhard Euler solved the Königsberg Bridge Problem (Euler, 1741). In this regard, a graph consists of a finite set of vertices (or nodes) that are connected by links called edges (or arcs). Following the emergence of promising results in electrical circuits and chemical structures in its early applications, graph theory has now become influential in addressing a large number of practical problems in other disciplines, such as transportation systems, social networks, big data environments, the internet of things, electrical power infrastructures, and biological neural networks (Boccaletti et al., 2006; Schweitzer et al., 2009; Watts and Strogatz, 1998).

The turning point of the complex brain network studies using graph theory goes back to the introduction of the “Human Connectome” (Sporns et al., 2005). In graph theory, an $N \times N$ adjacency matrix (also called a connection matrix) with the elements of zero or non-zero indicates the absence or presence of a relationship between the vertices of a network with $N$ nodes. By extracting different metrics from this matrix, one can obtain a topological analysis of the desired graph (e.g., the human brain network). A brain graph may be classified as either directed or undirected (Figure 2.2) based on whether the links between vertices carry directional information (e.g., causal interaction). Up to now, most human brain investigations have been devoted to the undirected networks because of the technical constraints surrounding the inference of directional networks (Liao et al., 2017).

A brain graph can also be categorized as either weighted or binary (Figure 2.2) based on whether the links between vertices can take different values. For instance, in a white matter anatomical network taken by diffusion MRI, we can obtain a weighted network using various information, such as fiber number, fiber length, and fractional anisotropy (Fornito et al., 2013; Zhong et al., 2015).

In 1998, Watts and Strogatz showed that many social, biological, and geoscience-based networks have a very striking organization, called “small-world” architecture, that makes them act as regular
networks, while they occasionally experience random activity (Watts and Strogatz, 1998). Small-world networks represent the shortest path between each pair of nodes in the network using the minimum number of edges. In small-world networks, the clustering coefficient (also referred to as transitivity) is high, and the average path length is short. These two characteristics are the result of a natural process to satisfy the balance between minimizing the resource cost and maximizing the flow of information among the network components (Bassett and Bullmore, 2006; Bullmore and Sporns, 2012; Farahani et al., 2019b; Chen et al., 2013; Meunier et al., 2010; Samu et al., 2014). Liao et al. (2017) explained in detail why the human brain network is expected to have a small-world architecture. The metabolic and wiring costs in connections among anatomically adjacent brain areas are lower than those among distant brain regions (Bullmore and Sporns, 2012).
Theoretical examinations have pointed out that the brain regions are more likely to interact with their neighboring areas to reduce the whole metabolic costs, while at the same time they need to have a small number of long-distance connections among themselves to accelerate data transmission (Bullmore and Sporns, 2012; Chen et al., 2013; Karbowski, 2001; Sik et al., 1995; Vértes et al., 2012). In agreement with theoretical studies, empirical investigations have also proved the dispersion of a few long connections among a plethora of short connections in the human brain network (Hagmann et al., 2007; He et al., 2007; Salvador et al., 2005).

The main capability of graph theory in neuroscience studies is usually unveiled after the construction of a functional brain network. Several measures can be used to assess the topological patterns of different networks such as clustering coefficient, modularity, average path, small-worldness, assortativity, and node centrality, which have been described in detail (Sporns et al., 2004; van den Heuvel et al., 2008). Typically, one cannot claim which measures are more suitable for studying the brain network (Bullmore and Sporns, 2009), but given the complex structure of the human brain, measures that can represent the small-world properties of the brain network are of great importance (He and Evans, 2010; Liao et al., 2017). This critical property arises with the help of hubs (i.e., highly connected nodes in a network), causing the creation of local clusters (Bullmore and Sporns, 2009; Jain, 2011). In the following, we discuss how to build a brain connectivity network using fMRI data and then explain the main measures that can be extracted from the brain network with the help of graph theory.

Applications of Graph Theory in Human Brain Connectivity using fMRI

Deeper overview on the leading applications of graph theory in cognitive and behavioral topics, as well as different neurological and psychiatric illnesses are provided in two separate subsections. Considering the weaknesses and strengths of these implications provides an insight into how to
utilize graph measures to make neurobiological inferences regarding the mechanisms underlying neuronal dynamics, in line with our research questions.

Sample size across reviewed studies ranged from 5 to 763 participants. The mean, mode, median, and standard deviation for the participants in all the study samples were 116.73, 40, 60, and 158.87, respectively. The included studies were published from 1998 to 2018 and organized into three taxonomies (Figure 2.3). The first group deals with the topological concepts of graph theory for the discovery of the brain as a large and complex network, which account for 34% of the selected articles. Then, papers that have applied graph theory in terms of human cognition and behavior for quantifying or comparing connectivity patterns in the brain network have been considered, accounting for 26% of the selected articles. Finally, applications of graph theory in mental disorders were reported, which account for 40% of the selected papers. In particular, the detailed frequency and percentage of the referenced papers in the last two categories are shown, separately.

Figure 2.3: Categorization of the reviewed studies.
Recent advances in neuroimaging modalities combined with graph theoretical approaches have opened new avenues toward studying the neural mechanisms underlying human cognition and behavior from the view of interregional brain interactions (Farahani et al., 2019b; Kriegeskorte and Douglas, 2018; Medaglia et al., 2015; Park and Friston, 2013; Pessoa, 2014; Petersen and Sporns, 2015; Sporns, 2014). Cognition involves a range of neuronal actions for knowledge assimilation and integration through thinking, experience, and the senses. Cognition contains manifestations of attention, comprehension, memory, decision making, reasoning, judgment, and executive functions (Mesulam, 1998). In the following, some of the applications of graph theory are presented in revealing human behavioral and cognitive performance, as well as the role of different large-scale brain networks in various conditions.

Human Intelligence and Brain Topology

Human intelligence refers to the marvelous and subtle function of human cognition, which is generally characterized by complex reasoning, conceptual thinking, and learning swiftly from experiences (Guilford, 1967). An early review of brain imaging studies has linked human intelligence to the structure and function of spatially distributed regions (Jung and Haier, 2007), indicating the possible importance of interactions between several regions, particularly in the frontal and parietal areas. Recently, many studies have focused on the relationship between general intellectual ability and small-world characteristics in intrinsic functional networks for describing individual differences in general intelligence (Hilger et al., 2017a; Langer et al., 2012; Van Den Heuvel et al., 2009). According to these studies, better intellectual performance was associated with shorter characteristic path length, the nodal centrality of hub regions in the salience network, as well as the efficiency of functional integration between the frontal and parietal areas (Jung and Haier, 2007).
Through an analysis of rs-fMRI data, Wu et al. (2013) illustrated that intelligence quotient is positively correlated with nodal properties in the attention-related network and is negatively correlated with nodal properties in the default mode, emotion, and language systems. However, although these findings suggest that general intelligence is profoundly affected by the functional integration of spatially distributed regions, they could not provide sufficient information as to whether and how human intellectual performance is associated with the brain’s modular architecture. To address this issue, Hilger et al. (2017b) proposed that intelligence involves the nodal characteristics of functional connectivity within and between different brain modules (especially in the parietal and frontal areas), not global modularity properties or whole-brain ratios of distinct node types.

**Topological Changes across the Lifespan**

The human brain goes through remarkable functional changes during the lifespan, from birth to adulthood. Modeling the lifetime trajectory of the functional connectome, multiple studies detected striking age-related alterations in highly connected hub areas mainly within the default mode, attentional, sensorimotor, and visual regions via rs-fMRI (Betzel et al., 2014; Cao et al., 2014b; Finotelli et al., 2018; Fransson et al., 2011; Gozdas et al., 2018; Grayson and Fair, 2017; Hwang et al., 2013; Meunier et al., 2009; Wu et al., 2013). Most of them also reported that local efficiency and the rich club coefficient (a metric that measures the extent to which well-connected nodes also connect to each other) were incremental until adulthood in healthy subjects and then dropped with aging, while global efficiency remained almost unchanged over the lifetime regardless of the early years after birth (Gao et al., 2011). Cao et al. (2014b) further identified changes in the number and strength of connections that were created to achieve an optimal balance between the wiring costs and communication efficiency over the lifespan (Bullmore and Sporns, 2012).

Moreover, inverse trajectories of change between long and short connections suggest a continuous
reorganization in the functional brain network with aging, leading to significant behavioral and cognitive differences throughout an individual’s life. Regarding modularity, there are somewhat mixed findings. Some have argued for little change in modularity during brain development (Fair et al., 2009) and aging (Meunier et al., 2009), while Cao et al. (2014b) reported a linear downward trend. In this regard, combining other functional neuroimaging techniques, as well as performing structure-function studies, will help elucidate the neural substrates underlying cognitive and behavioral differences during developmental stages (Shah et al., 2018).

**Working Memory Performance and Network Efficiency**

Working memory is a psychological construct for the temporary storage and manipulation of the information required to perform intricate cognitive tasks such as reasoning and decision-making (Diamond, 2013). Stanley et al. (2015) compared the functionality of working memory between young and older adults in an n-back experiment by quantifying the local and global measures in their brain networks. They demonstrated that lower local efficiency corresponds to the better performance of working memory in both groups. In contrast, increasing global efficiency has been correlated with high functionality in young adults but with a slight deficiency in older adults. Seeking to prove the right intraparietal sulcus as an area responsive to manipulations of working memory load, Markett et al. (2018) used rs-fMRI to show that centrality measures in this region correlate inversely with working memory capacity. In another fMRI study, Gong et al. (2016) analyzed how active learning from action video games affected the neuroplasticity of the brain by testing the integration of working memory- (central executive) and attention-related (salience) neural networks. By assessing the graph theoretical properties between advanced and amateur players, they revealed that long-term playing would enhance the functional integration within and between working memory and attention systems.
Effect of Cognitive Loads on the Brain Modularity

In the last decade, studies on dynamic reconfiguration of human brain topology during different cognitive tasks have attracted widespread attention. Researchers believe that such functional brain networks adapt flexibly to their cognitive demands while preserving the modular structure (Bassett et al., 2011; Braun et al., 2015; Fornito et al., 2012a; Liang et al., 2016). In the course of dynamic reorganization, the parietal and frontal brain regions that hold several connector (inter-modular) hubs are discerned to play crucial roles by regulating their brain-wide connections (Braun et al., 2015; Cole et al., 2013). For instance, intensifying cognitive loads during a working memory task is associated with increased integration between different modules of the brain network (Braun et al., 2015; Kitzbichler et al., 2011; Liang et al., 2016). Furthermore, flexibility and the inter-modular integration of frontal areas are associated with high performance on working memory tasks (Braun et al., 2015).

Regarding mental state analysis, notable studies have shown that modularity corresponds negatively to the level of consciousness by comparing the functional brain network in individuals who experienced non-rapid eye movement sleep and those in wakefulness (Boly et al., 2012; Tagliazucchi et al., 2013). The common point of all these findings is that an increased cognitive load or consciousness level brings about greater global integration of the neural networks (i.e., reducing the modularity coefficient). However, further studies are needed to make this claim more robust.

Role of Default Mode Network in Behavioral Performance

Comparing the brain topological alterations during a cognitive task and resting-state using fMRI data helps identify areas that affect human behavioral performance. DeSalvo et al. (2014) used a graph-based approach to explore variations in functional brain organization during semantic de-
cision making compared with rest in healthy participants. They observed that differences were generally associated with the language-related and DMN regions. More importantly, they found greater intra-modular communication in these regions during decision making (i.e., a decrease in distributed connectivity), whereas the inter-modular communication was stronger at rest.

Moreover, Lin et al. (2016) analyzed whether cognitive behavior correlates with the functional connectivity of the DMN in healthy subjects, both while at rest and during an attentional task. Quantifying the static and dynamic nodal properties within the DMN, they revealed the importance of the default network, especially the posterior cingulate areas, on human cognitive performance. Similarly, in a sustained attention paradigm, Farahani et al. (2019a) found significant local alterations during sleep deprived session compared to the rested wakefulness session across the default mode network. Finally, Sadaghiani et al. (2015) investigated the relationship between ongoing alterations in baseline connectivity patterns and behavioral performance through a continuous auditory detection task. Interestingly, their results indicated a reduction in modularity (i.e., increasing integration efficiency) before misses compared with hits and task-free rest, mostly in the DMN areas and visual networks. These findings augment our understanding about the key role of the DMN in behavioral performance at rest and during a task; however, its association with other brain regions in more complex cognitive tasks, such as reasoning and executive functions, requires further studies.

Behavioral Performance in Natural Environments and Everyday Settings

One of the fascinating areas of cognitive neuroscience in recent years is neuroergonomics; that is to say, the behavioral analysis of the human brain performance with regard to environments, work, technology, and everyday settings (Parasuraman and Rizzo, 2008). Qian et al. (2013) studied the topological changes of the brain connectome during passive hyperthermia using rs-fMRI data.
Despite maintaining economic small-worldness in both normal and hyperthermia conditions, the brain networks of heat-exposed subjects exhibited decreased clustering coefficients, as well as decreased local efficiency and small-worldness indices, suggesting a tendency toward a random network. They also conducted an attention network test (ANT). Their findings were highly relevant to global measure alterations and prefrontal local efficiency, indicating behavioral disorders during environmental heat exposure in executive attention but not in alerting or orienting.

Furthermore, functional imaging analyses on mental fatigue have indicated that declines in performance from fatigue are associated with brain topological alterations such as a decrease in small-world properties and global efficiency, as well as functional changes in the fronto-parietal network and connected areas in the thalamus and the striatum (Petruo et al., 2018). In particular, graph-based investigations using fMRI data express that long-range connectivity is changed when the effects of fatigue appear (Sun et al., 2017, 2014). For instance, Sun et al. (2017) studied the effects of a mid-task break on enhancing local efficiency and reported no significant impact of rest breaks on task performance. In general, such studies help to understand the neural mechanisms of fatigue; thus, by adopting a suitable recovery approach, one can try to improve human performance during cognitive tasks.

**Neurological and Psychiatric Disorders**

Disconnection in a brain made up of localized but linked specialized regions results in functional impairment, associating with atypical integration of distributed brain areas. Catani and ffytche (2005) elaborated the rises and fall of disconnection syndromes and pointed out that many neurological disorders can be explained via these syndromes, in line with the studies of pioneers in neurology and psychiatry such as Meynert, Wernicke and Dejerine. Studies in the field of complex brain networks have demonstrated that analyzing the network properties and metrics derived
from brain topology using rs-fMRI can help neurologists distinguish patient groups from control subjects in mental disorders (Bassett and Bullmore, 2009; Stam, 2014; Wang et al., 2010; Zhou et al., 2017). In the following, several studies that have used graph theory to investigate common neurological disorders, comprising epilepsy, Alzheimer’s disease (AD), multiple sclerosis (MS), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), are discussed. However, other mental disorders were also found in recent graph-based literature, including schizophrenia, Parkinson’s disease, chronic sleep restriction, insomnia, major depression, obsessive compulsive disorder (OCD), borderline personality disorder (BPD), and bipolar disorder (Algunaid et al., 2018; Armstrong et al., 2016; Farahani et al., 2019a; Díez-Cirarda et al., 2018; Kambeitz et al., 2016; Li et al., 2018; Manelis et al., 2016; Xu et al., 2016; Zhi et al., 2018), but their contribution is negligible and more attention is required in future research.

Epilepsy

Epilepsy is a chronic neurological disorder that is accompanied by aberrations in brain activity, resulting in recurring seizures and occasionally loss of consciousness (Hauser, 1990). Temporal lobe epilepsy (TLE) is the most prevalent form of epilepsy with partial seizures (Bernhardt et al., 2015). In two interesting rs-fMRI studies using network analysis, Výtvarová et al. (2017) and Dong et al. (2016) described the contribution of basal ganglia thalamocortical circuitry to the whole-brain functional connectivity in TLE. Although the detection and removal of epileptogenic lesions are necessary for the abolition of seizures, many studies have shown that seizures in TLE originate from abnormalities in the epileptogenic network rather than from lesions (Cooray et al., 2016; Rosenow and Lüders, 2001); thus, seizure recurrence is observed following approximately 40% of epilepsy surgeries within 5 years (Spencer, 2002). Therefore, the application of graph theory, along with clinico-radiological findings, helps to better understand the network mechanisms behind a cognitive decline in focal epilepsies, particularly TLE, and offers promising diagnostic biomarkers.
Vlooswijk et al. (2011) examined small-world properties in patients with TLE using rs-fMRI. In contrast to healthy subjects, they found a disruption of both local segregation (opposed to Wang et al. (2014b)) and global integration in patients with epilepsy. They confirmed the association between the IQ score and information processing performance, whether it is specialized or serial. The correlation between average path length and intellectual capability has been indicated by other experiments as well (Van Den Heuvel et al., 2009). To conclude, these results support the hypothesis that localization-related epilepsy leads to cognitive impairments by inducing global changes in the brain network instead of a localized disruption only.

Apart from TLE, other types of epilepsy such as childhood absence epilepsy (CAE) and sleep-related hypermotor epilepsy (SHE) have recently been investigated by researchers (Evangelisti et al., 2018; Wang et al., 2017). CAE is a common generalized epilepsy syndrome with a presumed genetic cause, characterized by episodes of sudden, profound impairment of consciousness without loss of body tone, appearing in otherwise healthy school-aged children. Wang et al. (2017) compared centrality measures between CAE patients and healthy controls and hypothesized that hub nodes inside the DMN and thalamus in CAE patients were clearly damaged. In other work, Evangelisti et al. (2018) reported topological alterations mainly in basal ganglia and limbic system in SHE patients.

Alzheimer’s Disease

The AD is a chronic and progressive neurodegenerative disorder that leads to deficits in memory and cognitive brain functions (Albert et al., 2011). The AD can be described as a disconnection syndrome because of the altered structural and functional connectivity architecture of the brain in
those suffering from this disease (Pievani et al., 2011). Aging is naturally associated with some cognitive decline, but if this inefficiency is exacerbated in an individual’s brain, one could experience mild cognitive impairment (MCI), which is an intermediate phase between age-related cognitive decline and dementia (Petersen, 2001). Statistical surveys report that approximately 15% of adults over 65 years old experience MCI (amnestic MCI or non-amnestic MCI) and that more than half of these cases convert to dementia in five years (Farlow, 2009). Early detection of the AD in subjects with MCI can prevent the progression of these impairments via disease-modifying treatments (Allison et al., 2014). Fortunately, the combination of graph theory and rs-fMRI has been able to act as a disease biomarker and reveal large-scale disconnection that is present before onset of AD symptoms (Botha and Jones, 2018; Brier et al., 2014; Dai and He, 2014; Wang et al., 2013).

By examining the brain network characteristics on functional connectivity, researchers concluded that individuals with AD exhibited degeneration of specific brain hubs, reduced clustering coefficients and path lengths very close to the values of random networks (Dai et al., 2015; delEtoile and Adeli, 2017; Sanz-Arigita et al., 2010; Supekar et al., 2008), similar to the results of researchers who worked on other imaging modalities (de Haan et al., 2012, 2009; Jalili, 2017; Kim et al., 2015; Stam et al., 2009). Also, other studies revealed that cognitive impairment in the AD was associated with a weakness in modular interconnectivity and hubs destruction (Brier et al., 2014) and significant alterations within the default network (Toussaint et al., 2014; Zhong et al., 2014). These findings were in parallel with a global decrease in long-distance functional connections especially between frontal and caudal brain regions (Sanz-Arigita et al., 2010). On the whole, the degeneration and randomization of the brain functional architecture in patients with AD indicates a great loss of global information integration. These results are highly associated with the anterior-posterior disconnection phenomenon and its role in the AD.

Moreover, authors combined graph theoretical approaches with advanced machine learning meth-
ods (here, support vector machines) to explore functional brain network alterations and classify individuals with AD using rs-fMRI (Hojjati et al., 2017; Khazaee et al., 2016, 2015). Further, by conducting statistical analysis on the brain networks of individuals with MCI who converted to AD (MCI converter) and those with stable MCI (MCI non-converter), they identified areas underlying this conversion (Hojjati et al., 2017). To sum up, these papers highlighted the efficiency of combining graph theory and machine learning for early detection of AD based on rs-fMRI connectivity analysis.

Multiple Sclerosis

MS is a chronic, degenerative, and heterogeneous autoimmune disease of the central nervous system, leading to physical, mental, or psychiatric problems (Marrie, 2017). Functional recovery in MS is achieved by repair of damage through remyelination and functional reorganization, which are the striking hallmarks of this disease (Filippi and Agosta, 2009). Most studies of functional connectivity based on graph theory in MS include analysis of rs-fMRI data (Gamboa et al., 2014). In one such study, Schoonheim et al. (2014) sorted the brain regions of interest based on their connectivity patterns using eigenvector centrality mapping (ECM) and reported MS-related differences for centrality in specific regions. As a result, decreased ECM values in sensorimotor and ventral stream areas were associated with clinical disability. In contrast, the thalamus and posterior cingulate demonstrated increased centrality as well as higher connectivity to regions with low centrality. To this end, the authors suggested a rerouting of thalamic communications to overcome the continuous inflammatory activity.

In two other studies, Shu et al. (2016) and Liu et al. (2017b) compared the topological changes of functional connectome in individuals with clinically isolated syndrome (i.e., the earliest stage of MS) and MS patients. Their graph-based results indicated that disrupted network organization
emerged in the earliest stage of MS, with a lesser degree relative to MS. Also, the extent of network alterations was correlated with cognitive impairment and physical disability only in MS patients. Importantly, Eijlers et al. (2017) attempted to demonstrate how abnormalities in functional network hierarchy are related to cognitive impairment in MS patients. Patients were classified into three categories: cognitively impaired, mildly cognitively impaired, and cognitively preserved. The centrality indices indicated that the occipital, sensorimotor and hippocampal areas for all three patient groups became less central than healthy controls, while cognitively impaired patients displayed extensive centrality growth in areas making up the DMN compared to other groups. Their results can be interpreted as reflecting the hallmark alterations in functional networks of cognitively impaired patients with increased relative importance (centrality) of the DMN.

Taken together, major changes in topological parameters of the brain network have been observed in the sensorimotor, cingulate, and frontotemporal cortex, as well as in the thalamus (Eijlers et al., 2017; Faivre et al., 2016; Rocca et al., 2016; Schoonheim et al., 2014, 2015; Tewarie et al., 2015). The thalamus is often known as a relay organ between several cortical and subcortical regions, taking part in a large variety of neurological functions such as motor, sensory, integrative, and higher cortical functions (Minagar et al., 2013). Thus, thalamic degeneration may lead to cognitive dysfunction and physical disability in patients with MS, even in the early stages of the disease (Benedict et al., 2013).

**Autism Spectrum Disorder**

ASD is a complex neurodevelopmental disability characterized by difficulties in communication and behavior (Roux et al., 2012). The increasing prevalence of ASD over the last decade has underlined the need for medical assessment to identify the symptoms and signs of this disorder (Johnson et al., 2007). However, there are possible challenges in autism screening because of
the uncertainty associated with the symptoms and neurobiological properties (Ecker et al., 2013; Mastrovito et al., 2018). These properties lead to great heterogeneity in the subjects and are the reason for the spectrum of the disease (Jeste and Geschwind, 2014; Lenroot and Yeung, 2013).

The contribution of rs-fMRI studies based on graph theory for autism exploration is considerable (Di Martino et al., 2014; Kazeminejad and Sotero, 2019; Keown et al., 2017; Redcay et al., 2013; Rudie et al., 2013; van den Heuvel et al., 2017). Authors in (Keown et al., 2017; Rudie et al., 2013) compared the brain topology in patients with ASD and healthy controls. They concluded that modularity, clustering coefficient, and local efficiency are relatively reduced in ASD (i.e., inefficiency of information transmission in a particular module) while global communication efficiency is increased (shorter average path lengths). As another example, Redcay et al. (2013) observed an increase in betweenness centrality and local connections by analyzing the prefrontal brain areas in adolescents with ASD. Moreover, the structure of the hub nodes was significantly changed in ASD (Balardin et al., 2015; Itahashi et al., 2014). Altogether, abnormalities in the functional architecture of the autistic brain were reported in both local and global metrics. Considering the huge discrepancies between subjects regarding local parameters (Finn et al., 2015), it was unclear whether such local parameters can be applied alone as a biomarker for ASD screening. To answer this question, Sadeghi et al. (2017) examined both local and global parameters extracted from rs-fMRI data and observed that distinctive features were only among the local parameters.

**Attention-deficit/hyperactivity Disorder**

ADHD affects about 3% to 5% of children globally (Nair et al., 2006). Wang et al. (2009b) were the first to explore the spontaneous connectivity patterns of whole-brain functional network in patients with ADHD and healthy controls using graph analysis of rs-fMRI. They reported that the functional networks in both groups represented an economic small-world behavior. However,
the brain networks of ADHD children exhibited more-regular configurations with higher local efficiency and a trend toward decreased global efficiency relative to healthy subjects, indicating a developmental delay of whole-brain functional networks in this pathology (Cao et al., 2016, 2014a, 2013; van den Heuvel et al., 2017; Wang et al., 2009b). In addition, by testing nodal properties, Wang et al. (2009b) claimed that areas such as medial prefrontal, temporal, and occipital cortices experienced regional loss of efficiency, while increased nodal efficiency was found in the inferior frontal gyrus.

Delayed maturation has further been reported in structural MRI studies (Hoogman et al., 2017), as well as in default network connectivity in youth with ADHD (Fair et al., 2010). Maturation rate differences between brain hemispheres may also characterize the ADHD brain, given significantly different interhemispheric asymmetry patterns recently observed in ADHD youths (Dutta et al., 2020; Douglas et al., 2018). Analyzing rs-fMRI, Fair et al. (2010) scrutinized interregional connectivity patterns within DMN and noticed decreased anterior-posterior connectivity in children with ADHD compared to healthy controls. In another study, Fair et al. (2013) conducted a regional connectivity analysis using degree index on the functional networks in children with two different ADHD presentations, i.e., inattentive and combined. While both subtypes exhibited some overlapping (particularly in the sensorimotor network), the combined ADHD exhibited atypical patterns in midline DMN components and the inattentive ADHD showed atypical connectivity within the dorsolateral prefrontal cortex and cerebellum. Contrary to the findings of children with ADHD, Cocchi et al. (2012) did not find any significant changes in global characteristics of the whole-brain functional networks in adults with ADHD compared to healthy controls.

Apart from the region-wise studies, Tomasi and Volkow (2012) computed the voxel-wise Pearson’s correlations across all pairs of brain voxels in ADHD children and healthy controls from the ADHD-200 database (Milham et al., 2012). Then, they classified the coefficients into long-range and short-range based on the anatomical distance, which was followed by constructing the cor-
responding functional connectivity density. As a result, they revealed that ADHD children had weaker interconnectivity (both long- and short-range) in the DMN, dorsal attention network, and cerebellum, and stronger short-range connectivity within reward network (ventral striatum and orbitofrontal cortex). Alterations in DMN have also been reported in studies applying non-negative matrix factorization (Anderson et al., 2014). In another study, Di Martino et al. (2013) observed similar centrality abnormalities within the precuneus in both ADHD and ASD groups, whereas ADHD patients exhibited particularly higher-degree centrality in the right striatum/pallidum. Finally, Colby et al. (2012) presented a machine learning approach using the combination of functional and structural graph-based features, as well as demographic information, to predict status of patients with ADHD from healthy children in the ADHD-200 database Milham et al. (2012).

By interpreting the above findings, it can be concluded that the functional connectomes of ADHD children had a tendency toward regular configurations (Wang et al., 2009b), while ADHD adults had no significant difference in terms of global architecture with healthy individuals (Cocchi et al., 2012). Also, disturbed nodal properties were identified in both children and adults, particularly in the attention, default-mode, sensorimotor, striatum, and cerebellum networks (Cocchi et al., 2012; Fair et al., 2010, 2013; Di Martino et al., 2013; Tomasi and Volkow, 2012; Wang et al., 2009b).

Research Gap and Rationale of the Study

In the scientific world, there is a significant data gap with respect to applying graph theory to investigate circadian fluctuations of functional networks using resting-state fMRI (rs-fMRI). In addition, there is limited functional MRI (fMRI) studies investigating the impact of time-of-day and chronotype on their results. Potentially, most studies assume that diurnal fluctuations of brain connectivity patterns as well as human chronotypes are relatively insignificant and are unlikely to lead to a substantial systematic bias into group analysis. Furthermore, previous resting-state
fMRI studies that have focused on circadian rhythms have yielded contradictory or sometimes even ambiguous findings (Blautzik et al., 2013; Cordani et al., 2018; Hodkinson et al., 2014; Jiang et al., 2016; Shannon et al., 2013; Steel et al., 2019), perhaps because of varying analysis pipelines. There are also inconsistencies in diurnal fluctuations of brain activation patterns in task-based fMRI studies (Gorfine and Zisapel, 2009; Marek et al., 2010).

To the best of our knowledge, this is the first resting-state fMRI study to assess circadian fluctuations of the whole-brain connectivity by using graph theory in both morning-type and evening-type individuals. Based on our systematic review (Farahani et al., 2019b) on the application of graph theory for identifying connectivity patterns in human brain network, the researchers’ interest in network neuroscience has increased dramatically during the last decade. To observe the evolution of the theme, Figure 2.4 displays the number of reviewed publications, year by year. This figure illustrates the researchers’ special attention to human connectome studies, especially the emerging role of graph analysis in topological explorations of the complex brain connections since 2009. Most articles are concentrated between 2009 and 2018 (92% of the selected publications), which is expected to increase dramatically in the next years. Interestingly, the Human Connectome Project (HCP) was launched in 2009 with the National Institutes of Health sponsorship, which is in line with these findings (Nih.gov, 2014). Thus, our current study is the first depicting functional connectivity alteration over the course of a day in subjects with extreme chronotypes using graph-theoretic analysis.

Moreover, Pareto analysis of the top keywords is shown in Figure 2.5. Obviously, the words “graph theory”, “fMRI”, “resting-state”, “functional connectivity”, and “small-world” were among the most used keywords in the reviewed papers (50% of the listed keywords). By this finding, it can be interpreted that those fMRI studies that have benefited from graph theory have: (a) been mostly carried out during resting-state than experimental task, which is in line with the HPC claim (Smith et al., 2013); (b) concentrated more on functional connectivity than effective connectivity;
(c) considered a pivotal role for the small-world phenomenon in constructing the human brain architecture.

It is important to note that, most previous studies that have applied graph theory to track alterations in brain activity are based on resting-state fMRI (Farahani et al., 2019b). However, some studies suggest that certain connectivity properties can be identified only by examining brain topology during task performance (Bilek et al., 2013; Pezawas et al., 2005). In this study, we will investigate the topological changes in resting-state brain functional connectivity patterns in both morning session and evening session. In general, the purpose of the current study is to detect global and local changes in the brain network topology over time-of-day, as well as the variations caused by the participants’ chronotypes. The findings might provide potential imaging markers of diurnal (circadian) rhythm in human brain network, affecting cognitive functions and a wide range of neurobehavioral events.
Finally, we should note that all previous studies in chronobiology domain concerned particular neuropsychological functions examined by performing specific tasks. Resting-state networks are mostly believed to remain stable throughout the day (Biswal et al., 2010; Byrne and Murray, 2017). An opposite view was postulated by Blautzik et al. (2013) and Park et al. (2012), who argued that the level of stability varies over a period of 1 day across different resting state networks, ranging from highly rhythmic to stable. Jiang et al. (2016) found that widespread brain areas exhibit diurnal variations in resting-state. However, the study’s sample size was relatively small (16 participants), and neither the subjects’ sleep-wake pattern nor chronotypes were controlled, which could have affect the results. In our research we used the chronotype-based paradigm (Schmidt et al., 2007). Thus, the goal of this study is to investigate circadian fluctuations of functional networks using...
resting-state fMRI (rs-fMRI).
CHAPTER 3: METHODOLOGY

Some of the material in this chapter, in the "Brain Network Construction" and "Computation of Graph Matrices" sections, is adapted from the paper by Farahani et al. (2019a) which has been published in the *Frontiers in Neuroscience*¹ journal.

Participants

The participants were recruited through online advertisements on the lab’s website and Facebook. 5354 volunteers participated in the first stage of selection and were asked to complete two questionnaires: the Chronotype Questionnaire (Oginska et al., 2017) for diurnal preferences assessment and the Epworth Sleepiness Scale (ESS; Johns, 1991) for daytime sleepiness measurements as well as the sleep-wake assessment (real versus ideal wake- and bedtimes). Individuals reporting excessive daytime sleepiness were excluded from the study, as determined by the cutoff points ESS (≤ 10 points) questionnaire. 451 subjects divided to morning or evening types were selected to PER3 VNTR polymorphism genotyping. DNA was isolated from buccal swabs using DNA GeneMATRIX Swab-Extract DNA Purification Kit (EURx, Gdańsk, Poland) following manufacturers protocol. VNTR polymorphism in PER3 gene was analyzed with PCR. 2µl of each DNA sample was amplified in the final reaction volume of 20µl containing: 2µl of 10x Pfu buffer (EURx, Gdańsk, Poland), 0.5U of Pfu polymerase (EURx, Gdańsk, Poland), 0.5µM of forward/reverse primer and 0.2mM dNTP mix. The primer sequences were following: forward 5′-TGTCTTTTTCATGTGCCCTTACTT- 3′; reverse 5′-TGTCCTGGCATTCAGTTG-3′. The cycle conditions were as follows: 35 cycles of denaturation at 94°C for 40s; annealing at 60°C for 30s; extension at 70°C for 40s. The initial denaturation and final extension were carried out at

94°C for 6 minutes and 70°C for 12 minutes. Following amplification, 8µl of each PCR reaction product was analyzed by electrophoresis in agarose gel (1.8% agarose, 0.5x TBE) stained with ethidium bromide and documented in a gel documentation system. Only the subjects that were homozygous for the PER3 4 (ET) and PER3 5 (MT) alleles were included for the study. Sixty-two healthy and young participants (39 women, mean age: 23.97 ± 3.26 y.o.) were selected for the analysis. The selection criteria included: age between 20 and 35 years, right-handedness as indicated by the Edinburgh Handedness Inventory (Oldfield et al., 1971), regular time-of-day schedule without sleep debt, no neurological or psychiatric disorders, no addiction, normal or corrected-to-normal vision, and no MRI contraindications.

The resting-state fMRI was performed twice – in the morning (MS) and evening (ES) sessions – about one and ten hours after wake-up, respectively. Participants were asked to maintain a regular sleep-wake schedule one week before study, controlled using MotionWatch 8 actigraphs. They wore actigraphs also during the study days for supervising their sleep length and quality. Furthermore, the night before the morning session, subjects slept in rooms located in the same building, as the MR laboratory. Individuals abstained from alcohol (48 h) and caffeine (24 h) before imaging sessions and could engage only in non-strenuous activities during study days. The study was approved by the Institute of Applied Psychology Ethics Committee of the Jagiellonian University. Informed, written consent was provided by all participants in accordance with the Declaration of Helsinki. Demographics, questionnaires and actigraphy results are provided in the Table 3.1.

MRI Data Acquisition

Magnetic resonance imaging was performed using a 3T Siemens Skyra MR System equipped with a 64-channel head coil. Anatomical images were obtained with the use of sagittal 3D T1-weighted
Table 3.1: Demographics, questionnaires and actigraphy results.

<table>
<thead>
<tr>
<th>Variables</th>
<th>MT (N = 31)</th>
<th>ET (N = 31)</th>
<th>Sign.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11/20</td>
<td>12/19</td>
<td>ns</td>
</tr>
<tr>
<td>Age (years)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24.45 ± 3.83</td>
<td>23.48 ± 2.55</td>
<td>ns</td>
</tr>
<tr>
<td>ME&lt;sup&gt;b&lt;/sup&gt;</td>
<td>15.71 ± 2.41</td>
<td>28.45 ± 2.39</td>
<td>*</td>
</tr>
<tr>
<td>AM&lt;sup&gt;b&lt;/sup&gt;</td>
<td>21.47 ± 3.58</td>
<td>22.26 ± 3.51</td>
<td>ns</td>
</tr>
<tr>
<td>ESS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.52 ± 2.48</td>
<td>5.87 ± 3.01</td>
<td>ns</td>
</tr>
<tr>
<td>EHI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>86.83 ± 12.92</td>
<td>89.19 ± 13.93</td>
<td>ns</td>
</tr>
<tr>
<td>VNTR of PER3</td>
<td>5/5</td>
<td>4/4</td>
<td></td>
</tr>
<tr>
<td>Declared waketime (hh : mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>07 : 07 ± 62 min</td>
<td>07 : 25 ± 48 min</td>
<td>ns</td>
</tr>
<tr>
<td>Declared bedtime (hh : mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23 : 24 ± 55 min</td>
<td>00 : 06 ± 49 min</td>
<td>*</td>
</tr>
<tr>
<td>Declared length of perfect sleep (hh : mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>08 : 50 ± 42 min</td>
<td>08 : 38 ± 54 min</td>
<td>ns</td>
</tr>
<tr>
<td>Actigraphy-derived waketime (hh : mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>07 : 43 ± 70 min</td>
<td>08 : 16 ± 69 min</td>
<td>ns</td>
</tr>
<tr>
<td>Actigraphy-derived bedtime (hh : mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23 : 58 ± 58 min</td>
<td>00 : 48 ± 58 min</td>
<td>*</td>
</tr>
<tr>
<td>Actigraphy-derived length of real sleep (hh : mm)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>07 : 53 ± 51 min</td>
<td>07 : 36 ± 40 min</td>
<td>ns</td>
</tr>
</tbody>
</table>

Abbreviations: MT morning types, ET evening types, ME morningness/eveningness scale (from Chronotype Questionnaire), AM amplitude scale (from Chronotype Questionnaire), ESS Epworth Sleepiness Scale, EHI Epworth Handedness Inventory, a chi-square test, b Mann-Whitney U test, c Student’s t-test, * p – value < 0.05, ns non-significant.

MPRAGE sequence. 10-minutes functional resting-state blood-oxygenation-level-dependent (BOLD) images were acquired using a gradient-echo single-short echo planar imaging sequence with the following parameters: repetition time (TR) = 1,800 ms; echo time (TE) = 27 ms; field of view (FOV) = 256 × 256 mm²; slice thickness = 4 mm; voxel size = 4 × 4 × 4 mm³, with no gap. A total of 34 interleaved transverse slices and 335 volumes were acquired from eligible subjects. During the resting state procedure, participants were instructed to lie in the scanner with eyes open while thinking of nothing, and remaining awake throughout the scanning session. Participants’ awareness was monitored using an eye tracking system (Eyelink 1000, SR research, Mississauga, ON, Canada).
Data Pre-processing

Data preprocessing was performed using DPABI v. 4.2 and SPM 12 both working under Matlab v.2018a (The Mathworks Inc.). Due to the signal equilibration, first 10 time points were discarded. Subsequently, slice timing and realignment with assessment of the voxel specific head motion were conducted. The subjects with movements in one or more of the orthogonal directions above 3 mm or rotation above 3° were discarded from the analysis. As the result, the total of four participants were excluded due to the excessive head movements. Then, functional scans were coregistered using T1 images and normalized to Montreal Neurological Institute (MNI) space using DARTEL and voxel size of 3 × 3 × 3 mm³. Altogether, seven participants were excluded due to the low quality of the normalization. The functional data was spatially smoothed with 4 mm Full Width at Half Maximum (FWHM) kernel. The 24 motion parameters, which were derived from the realignment step were regressed out from the functional data by linear regression as well as five principal components from both cerebrospinal fluid and white matter signals using principal components analysis integrated in a Component Based Noise Correction Method (Behzadi et al., 2007). The global signal was included due to its potential in providing the additional valuable information (Liu et al., 2017a) and the signal was band-pass filtered (0.01 – 0.1 Hz).

Brain Network Construction

By considering the human brain as a large-scale and complex network, graph-based methods help to analyze the human connectome by providing a mathematical representation of pairwise relations between brain regions of interest (ROIs). An overview of our analysis pipeline is shown in Figure 3. First, fMRI data will be collected for all subjects and underwent standard pre-processing with the SPM12 package (http://www.fil.ion.ucl.ac.uk/spm), which included slice timing correction, re-
alignment, image coregistration, normalization based on segmentation, and spatial smoothing. The data will then be aligned to an automated anatomical labeling (AAL) atlas, which is used to define ROIs (i.e., graph nodes) for brain network construction. The AAL atlas parcels the entire brain into 116 distinct anatomical units (Tzourio-Mazoyer et al., 2002), including 90 cortical and subcortical areas (regions 1–90) as well as 26 cerebellar areas (regions 91–116). The representative time course of each region will then be extracted by averaging BOLD signals across all voxels in the region. Then, by means of Pearson’s correlation coefficient, the functional connectivity between each pair of ROIs was computed. To improve the normality, the correlation values were converted into z values using Fisher’s r-to-z transformation. At this stage, a symmetrical FC matrix (adjacency matrix) with a size of 116×116 was constructed for each subject. Given the controversy over the use of negative correlations (Schwarz and McGonigle, 2011; Wang et al., 2011), we confined the analysis to positive correlations and set the negative coefficients to zero.

The calculation of most graph measures requires sparse matrices (Power et al., 2011; Wang et al., 2010). To exclude the confounding effects of spurious links in interregional connectivity matrices (Power et al., 2011), we adopted a thresholding procedure based on network density to preserve a ratio of the strongest connections and remove weaker connections (van den Heuvel et al., 2017). This procedure leads to equal network density across all subjects (i.e., equal number of edges), which is essential to compare network topology within or between participants (Gamboa et al., 2014). The sparsity threshold we used in this study range from 0.05 to 0.275 with an interval of 0.025, which has been shown to well prevent the formation of disconnected or densely connected networks (Wang et al., 2020). This step is followed by binarizing the thresholded matrices to make the computational complexity more tractable and increase the transparency of network properties (Figure 3.2).
Figure 3.1: Schematic representation of brain network construction and graph theoretical analysis using fMRI data. After processing (B) of the raw fMRI data (A) and division of the brain into different parcels (C), several time courses will be extracted from each region (D) to create the correlation matrix (E). To reduce the complexity and enhance visual understanding, the binary correlation matrix (F) and the corresponding functional brain network (G) will be constructed, respectively. Eventually, by quantifying a set of topological measures, graph analysis will be performed on the brain’s connectivity network (H). Adapted from Farahani et al. (2019b).

Computation of Graph Metrics

Using binary undirected matrices, we examined the topological properties of functional brain network for each participant (across a range of cost thresholds) at both global and local levels with the Brain Connectivity Toolbox (BCT, http://www.brain-connectivity-toolbox.net/; Rubinov and Sporns, 2010) and Graph Theoretical Network Analysis Toolbox (GRETNA; Wang et al., 2015). Global measures primarily aimed at revealing the functional segregation and integration of the brain network include global efficiency ($E_{glob}$), local efficiency ($E_{loc}$), mean clustering coeffi-
Correlation matrices (transformed Fisher’s r-to-z) and 10% thresholded and binarized matrices for the morning (A and C) and evening (B and D) sessions (averaged across all participants in each session).

Cp, average shortest path length (Lp), modularity (Q) and small-world attributes (σ). Local properties are calculated for each individual node (region) separately, reflecting the nodal centrality and density of hubs (either connector or provincial) in the network. In this study, we calculated the most common local properties such degree centrality, clustering coefficient, modularity, shortest path length, local efficiency, betweenness centrality and participant coefficient (Rubinov and Sporns, 2010).
Global Measures

Graph metrics can be classified into two main categories: global and local measures. Global measures (Figure 3.3) are primarily aimed at revealing the functional segregation (e.g., clustering coefficient, modularity, and transitivity; Figure 3.3A) and integration (e.g., characteristic path length and global efficiency; Figure 3.3B) of information flow in brain networks, and were therefore computed here. The small-world property displays an optimal balance between network segregation and integration (Figure 3.3C). In addition to global descriptors of segregation and integration, we calculated assortativity (Figure 3.3D), a global metric that reflects network resilience to random or deliberate failures (Bullmore and Bassett, 2011; Farahani et al., 2019b; Rubinov and Sporns, 2010).

Local Measures

On the other hand, local measures (Figure 3.4) in human brain functional networks mainly provide insight into the nodal centrality and density of hubs. In network neuroscience, hubs (either connector or provincial; Figure 3.4A) are thought to play a key role in transferring signals among brain regions during resting and task states (Liang et al., 2013). Connector hubs interconnect nodes belonging to different modules, and provincial hubs are responsible for linking the nodes in the same module (He et al., 2009; Power et al., 2013). We calculated the most widely used local graph measures for evaluating the nodal centrality and detecting hubs in a network (Figure 3.4B), including the nodal degree, betweenness centrality, closeness centrality, participation coefficient, diversity coefficient, subgraph centrality, $K$-coreness centrality, PageRank centrality, and eigenvector centrality (Boccaletti et al., 2006; Rubinov and Sporns, 2010; Farahani et al., 2019b; Zuo et al., 2012).
Figure 3.3: Summary of global graph measures. (A) Segregation measures include the clustering coefficient, which computes the extent to which the neighbors of a given node are interconnected, and modularity, which reflects clusters of densely interconnected nodes with sparse connections among other clusters. (B) Integration measures include the characteristic path length, which quantifies the potential for information transmission and is determined as the average shortest path length between nodes. (C) Small-worldness is dedicated to graphs in which most nodes are not neighbors but can be reached by any other node with the minimum possible path length. Small-world networks exhibit an intermediate balance between regular and random networks (i.e., they consist of many short-range links alongside a few long-range links), thus reflecting a high clustering coefficient and a short path length. (D) The assortativity index measures the extent to which a network can resist failures in its main components. Adapted from Farahani et al. (2019b).
Figure 3.4: Summary of global local measures. (A) Hubs refer to nodes with a high nodal centrality, which are classified as connector or provincial. (B) Network centrality measures: degree centrality (the number of node’s neighbors), betweenness centrality (the ratio of all shortest paths in the network that contain a given node), closeness centrality (the average of the shortest paths from a given node in a connected graph to every other nodes), eigenvector centrality (a self-referential index which computes the centrality of a node based on the centrality of its neighbors; here, the red node is more central than the gray node while their degrees are equal), participation coefficient (the distribution of a node’s connections across its communities), and PageRank (a variant of eigenvector centrality that is used by Google Search to determine a page’s importance). The size of the nodes in all cases is proportional to the node degree, and the red nodes (except in the eigenvalue centrality) are the most central with respect to the corresponding definition of centrality, even though their degrees are low. Adapted from Farahani et al. (2019b).
CHAPTER 4: RESULTS

Global Properties

Among the global measures examined, significant differences were found in the small-worldness and network synchronization between morning and evening sessions (Figure 4.1). Figure 4.1A depicts that small-worldness decreased with higher sparsity in both sessions. Compared to the morning session, the evening session showed relatively higher small-worldness at sparsity 0.15 to 0.275 ($p<0.05$, Bonferroni corrected), whereas the alterations were not significant in terms of chronotypes. Furthermore, analyzing the synchronization (Figure 4.1B), which examines how network nodes fluctuate in the same wave pattern, demonstrated an increasing trend as the threshold sparsity increased in both sessions. Contrast analysis showed that the synchronization was significantly higher under evening session than morning session at sparsity 0.125 to 0.275 ($p<0.05$, Bonferroni corrected) but no compelling evidence of changes by people’s chronotypes.

Local Properties

Table 4.1 summarizes the results of the paired t-test for a set of nodal/local properties (including degree centrality, betweenness centrality, clustering coefficient, and nodal efficiency) of all statistically significant brain regions within time-of-day. Here, we calculated the areas under the curve (AUC) for each mentioned network measure to provide a scaler that does not depend on a specific threshold selection (Wang et al., 2009a; Zhang et al., 2011). According to Table 4.1, numerous significant alterations are evident between the morning and evening sessions mostly across the left hemisphere in areas such as precentral gyrus, orbital part of inferior frontal gyrus, lentiform nucleus (particularly the putamen), inferior temporal gyrus, and a series of regions inside the cere-
Figure 4.1: Results of paired T-test on the small-worldness at the threshold values of 0.05 to 0.275 (A). Results of paired T-test on the synchronization at the threshold values of 0.05 to 0.275 (B).

bellum. We did not find any significant differences in clustering coefficient and shortest path length between the two sessions \((p>0.05)\).
Table 4.1: List of brain ROIs that changed throughout the day (p-values are adjusted for the Bonferroni correction so any value < 0.05 is statistically significant)

<table>
<thead>
<tr>
<th>ROI (modules)</th>
<th>MNI Coordinates</th>
<th>AAL label</th>
<th>Degree Centrality</th>
<th>Betweenness Centrality</th>
<th>Clustering Coefficient</th>
<th>Nodal Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (DMN)</td>
<td>-38.65 -5.68 50.94</td>
<td>Precentral_L</td>
<td>0.0213</td>
<td>0.0107</td>
<td></td>
<td>0.0120</td>
</tr>
<tr>
<td>3 (DMN)</td>
<td>-18.45 34.81 42.20</td>
<td>Frontal_Sup_L</td>
<td>0.0200</td>
<td></td>
<td></td>
<td>0.0226</td>
</tr>
<tr>
<td>15 (FPN)</td>
<td>-35.98 30.71 -12.11</td>
<td>Frontal_Inf_Orb_L</td>
<td>0.0215</td>
<td>0.0018</td>
<td></td>
<td>0.0126</td>
</tr>
<tr>
<td>19 (SMN)</td>
<td>-5.32 4.85 61.38</td>
<td>Supp_Motor_Area_L</td>
<td>0.0075</td>
<td></td>
<td></td>
<td>0.0052</td>
</tr>
<tr>
<td>54 (VN)</td>
<td>38.16 -81.99 -7.61</td>
<td>Occipital_Inf_R</td>
<td></td>
<td></td>
<td>0.0152</td>
<td></td>
</tr>
<tr>
<td>61 (FPN)</td>
<td>-42.80 -45.82 46.74</td>
<td>Parietal_Inf_L</td>
<td>0.0214</td>
<td></td>
<td></td>
<td>0.0210</td>
</tr>
<tr>
<td>63 (SMN)</td>
<td>-55.79 -33.64 30.45</td>
<td>SupraMarginal_L</td>
<td>0.0326</td>
<td></td>
<td></td>
<td>0.0224</td>
</tr>
<tr>
<td>65 (FPN)</td>
<td>-44.14 -60.82 35.59</td>
<td>Angular_L</td>
<td></td>
<td></td>
<td>0.0020</td>
<td></td>
</tr>
<tr>
<td>73 (LS)</td>
<td>-23.91 3.86 2.40</td>
<td>Putamen_L</td>
<td>0.0013</td>
<td>0.0216</td>
<td></td>
<td>0.0014</td>
</tr>
<tr>
<td>77 (LS)</td>
<td>-10.85 -17.56 7.98</td>
<td>Thalamus_L</td>
<td>0.0218</td>
<td></td>
<td></td>
<td>0.0232</td>
</tr>
<tr>
<td>78 (LS)</td>
<td>13.00 -17.55 8.09</td>
<td>Thalamus_R</td>
<td></td>
<td></td>
<td>0.0072</td>
<td></td>
</tr>
<tr>
<td>86 (DMN)</td>
<td>57.47 -37.23 -1.47</td>
<td>Temporal_Pole_Sup_L</td>
<td>0.0076</td>
<td>0.0300</td>
<td></td>
<td>0.0055</td>
</tr>
<tr>
<td>89 (VN)</td>
<td>-49.77 -28.05 -23.17</td>
<td>Temporal_Inf_L</td>
<td>0.0141</td>
<td>0.0333</td>
<td></td>
<td>0.0148</td>
</tr>
<tr>
<td>90 (VN)</td>
<td>53.69 -31.07 -22.32</td>
<td>Temporal_Inf_R</td>
<td>0.0313</td>
<td>0.0409</td>
<td></td>
<td>0.0348</td>
</tr>
<tr>
<td>91 (CRB)</td>
<td>-35.00 -67.00 -29.00</td>
<td>Cerebellum_Crus1_L</td>
<td>0.0057</td>
<td>0.0187</td>
<td></td>
<td>0.0114</td>
</tr>
<tr>
<td>92 (CRB)</td>
<td>38.00 -67.00 -30.00</td>
<td>Cerebellum_Crus1_R</td>
<td>0.0165</td>
<td>0.0480</td>
<td></td>
<td>0.0366</td>
</tr>
<tr>
<td>93 (CRB)</td>
<td>-28.00 -73.00 -38.00</td>
<td>Cerebellum_Crus2_L</td>
<td>0.0165</td>
<td>0.0480</td>
<td></td>
<td>0.0366</td>
</tr>
<tr>
<td>94 (CRB)</td>
<td>33.00 -69.00 -40.00</td>
<td>Cerebellum_Crus2_R</td>
<td>0.0165</td>
<td>0.0480</td>
<td></td>
<td>0.0366</td>
</tr>
<tr>
<td>101 (CRB)</td>
<td>-31.00 -60.00 -45.00</td>
<td>Cerebellum_7b_L</td>
<td>0.0177</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>103 (CRB)</td>
<td>-25.00 -55.00 -48.00</td>
<td>Cerebellum_8_L</td>
<td>0.0198</td>
<td>0.0400</td>
<td></td>
<td>0.0299</td>
</tr>
<tr>
<td>107 (CRB)</td>
<td>-22.00 -34.00 -42.00</td>
<td>Cerebellum_10_L</td>
<td>0.0261</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MNI Montreal Neurological Institute space, AAL Automated Anatomical Labeling atlas, SMN sensorimotor network, VN visual network, FPN frontoparietal network, DMN default mode network, LS limbic system, CRB cerebellar network.

Moreover, the results of AUC for degree centrality and betweenness centrality of all 116 brain regions are visualized in Figure 4.2A and Figure 4.2B, respectively. Red lines represent areas where diurnal variations are statistically significant. Compared with the morning session, the evening session showed significantly decreased degree centrality in the left precentral gyrus, dorsolateral part of left superior frontal gyrus, left supplementary motor area, supramarginal and angular gyri of the left inferior parietal lobe, left putamen, left thalamus, bilateral inferior temporal gyrus, and increased degree centrality in some areas within cerebellum (p<0.05, Bonferroni corrected).
Furthermore, there was compelling evidence of changes in modularity index between the two ses-
sions at sparsity 0.1 to 0.275 ($p<0.05$, Bonferroni corrected). Figure 4.3 illustrates the modular
properties of both sessions based on the mean connectivity matrix across all participants at a spar-
sity of 0.1. As is clear, the evening session has overall more modules than the morning session.

**Hub Analysis**

In this subsection, using a pre-determined modular classification, which includes the sensorimotor,
visual, frontoparietal, default mode, limbic, and cerebellar networks (Yeo et al., 2011), we
identified network hubs along with their types (i.e., connector or provincial) in both morning and
evening sessions (Table 4.2 and 4.3, respectively). The results are based on the mean connectivity
matrix (across all participants for each corresponding session) and network density of 0.1. Ac-
ccording to the Table 4.2 and 4.3, the identified hubs are almost overlapping in the morning and
evening sessions, except for minor changes in areas such as the left supramarginal gyrus, right
superior temporal pole, right thalamus, left lobule VIII of cerebellar hemisphere, and lobules IV,
V, and VI of vermis. The interesting thing about this table is how the hubs are distributed in the six
brain modules and the dominant type of hubs in each of these modules. For example, about 50%
of sensorimotor network nodes play a hub role in both morning and evening sessions, making this
module the densest part of the brain during resting state. Notably, most of sensorimotor hubs are
provincial (i.e., within modular connections), while hubs in default mode, limbic and cerebellar
networks are mainly connector (i.e., between modular connections).

To visualize the results, connectograms of both sessions are illustrated in Figure 4.4 by means of
Circos software (Krzywinski et al., 2009). Parcellated elements on the outermost circle indicate the
116 AAL brain areas marked with a unique RGB code and belong to one of the predefined mod-
ules (for clearer visualization, two hemispheres are separated). This outer circle circumscribes five
Table 4.2: Summary of module properties for the morning session (at a sparsity of 0.1). The type of hub, provincial or connector, is denoted by superscript $p$ or $c$, respectively.

<table>
<thead>
<tr>
<th>Modules</th>
<th>Degree Histograms</th>
<th>#Nodes</th>
<th>#Hubs</th>
<th>Hub Regions$^{(\text{Hub type})}$</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensorimotor Network</td>
<td><img src="image" alt="Sensorimotor" /></td>
<td>18</td>
<td>10(56%)</td>
<td>Rolandic Oper$^p$</td>
<td>Rolandic Oper$^p$</td>
<td>Insula$^p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postcentral$^p$</td>
<td></td>
<td>Postcentral$^p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SupraMarginal$^p$</td>
<td></td>
<td>SupraMarginal$^p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Temporal_Sup$^p$</td>
<td></td>
<td>Temporal_Sup$^p$</td>
</tr>
<tr>
<td>Visual Network</td>
<td><img src="image" alt="Visual" /></td>
<td>16</td>
<td>4(25%)</td>
<td>Lingual$^p$</td>
<td>Lingual$^p$</td>
<td>Fusiform$^p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fusiform$^p$</td>
<td></td>
<td>Fusiform$^p$</td>
</tr>
<tr>
<td>Frontoparietal Network</td>
<td><img src="image" alt="Frontoparietal" /></td>
<td>16</td>
<td>0(0%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Default Mode Network</td>
<td><img src="image" alt="Default" /></td>
<td>20</td>
<td>2(10%)</td>
<td>Precentral$^c$</td>
<td>Precentral$^p$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Limbic System</td>
<td><img src="image" alt="Limbic" /></td>
<td>20</td>
<td>3(15%)</td>
<td>Cingulum_Mid$^c$</td>
<td>Cingulum_Mid$^c$</td>
<td>Thalamus$^p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Cerebellar Network</td>
<td><img src="image" alt="Cerebellar" /></td>
<td>26</td>
<td>5(19%)</td>
<td>Cerebellum_4.5$^c$</td>
<td>Cerebellum_4.5$^c$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cerebellum_6$^c$</td>
<td>Cerebellum_6$^c$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
<td>—</td>
<td>Vermis_4.5$^p$</td>
</tr>
</tbody>
</table>

inner circular heatmaps created to represent the values of five distinct centrality measures. The range for each of these measures is from the minimum to maximum assumed value. Toward the center, these measures are degree centrality, participation coefficient, $K$-coreness centrality, eigenvector centrality, and PageRank. The values of all measures, as well as the functional connections
Table 4.3: Summary of module properties for the evening session (at a sparsity of 0.1). The type of hub, provincial or connector, is denoted by superscript $p$ or $c$, respectively.

<table>
<thead>
<tr>
<th>Modules</th>
<th>Degree Histograms</th>
<th>#Nodes</th>
<th>#Hubs</th>
<th>Hub Regions$^{(\text{Hub type})}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Left Hemisphere</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorimotor Network</td>
<td><img src="image" alt="Graph" /></td>
<td>18</td>
<td>9(50%)</td>
<td>Rolandic_Oper$p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insula$p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postcentral$p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SupraMarginal$c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Temporal_Sup$p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lingual$p$</td>
</tr>
<tr>
<td>Visual Network</td>
<td><img src="image" alt="Graph" /></td>
<td>16</td>
<td>4(25%)</td>
<td>Fusiform$p$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontoparietal Network</td>
<td><img src="image" alt="Graph" /></td>
<td>16</td>
<td>1(6%)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Default Mode Network</td>
<td><img src="image" alt="Graph" /></td>
<td>20</td>
<td>2(10%)</td>
<td>Precentral$c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limbic System</td>
<td><img src="image" alt="Graph" /></td>
<td>20</td>
<td>2(10%)</td>
<td>Cingulum_Mid$c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar Network</td>
<td><img src="image" alt="Graph" /></td>
<td>26</td>
<td>6(23%)</td>
<td>Cerebellum_4_5$c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cerebellum_6$c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cerebellum_8$c$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

in each of the connectograms, are derived from the average of all individuals in the corresponding session. The red and black curves show the functional connections between and within modules, respectively. An unambiguous abbreviation scheme was created to label each parcellation, as summarized in Appendix Table A.1.
Correlation Analysis

The purpose of performing correlation analysis is to investigate whether global and local measures are significantly correlated with the variable of interest (e.g., ME scale, AM scale, ESS, or any other cognitive/behavioral variables) across subjects while controlling the differences of the covariates of no interest (e.g., age, gender, and clinical variables). The results of correlation analysis for morning and evening sessions are shown in Tables 4.4 and 4.5, respectively. Clearly, most of the correlations are related to the morning session rather than the evening session.

According to Table 4.4, partial correlation analysis revealed significant negative associations between AM score and mean clustering coefficient, network local efficiency, and average path length ($p<0.05$, Bonferroni corrected). Findings also showed significant negative associations between ME score and a series of nodal properties of right hippocampus and right parahippocampal gyrus, as well as positive associations between ME score and nodal metrics (here, degree and nodal efficiency) of right lenticular nucleus, pallidum. Furthermore, we found significant positive associations between AM score and nodal metrics (here, degree and nodal efficiency) of left precentral gyrus and left postcentral gyrus, as well as negative associations between AM score and degree and betweenness centrality of right lobule X of cerebellum. Finally, the only significant correlation around ESS score was its positive associations with degree and nodal efficiency of left postcentral gyrus.

As indicated in Table 4.5 (evening session), we found significant positive associations between ME score and assortativity and average path length ($p<0.05$, Bonferroni corrected). Results also showed significant negative associations between AM score and nodal metrics (here, nodal clustering coefficient and local efficiency) of right hippocampus, as well as positive associations between ME score and degree centrality of right pallidum. Furthermore, positive and negative correlations were observed for ME and AM, respectively, with nodal metrics within the left parahippocampal
Table 4.4: Morning session - partial correlations between global and nodal metrics with ME, AM, and ESS scores \((n = 62)\). The significance level is set at a \(p < 0.05\) and adjusted for the Bonferroni correction.

<table>
<thead>
<tr>
<th></th>
<th>ME</th>
<th>AM</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Metrics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clustering Coefficient</td>
<td>—</td>
<td>(-0.328(0.041))</td>
<td>—</td>
</tr>
<tr>
<td>Network Local Efficiency</td>
<td>—</td>
<td>(-0.434(0.011))</td>
<td>—</td>
</tr>
<tr>
<td>Average Path Length</td>
<td>—</td>
<td>(-0.320(0.045))</td>
<td>—</td>
</tr>
<tr>
<td><strong>Nodal Metrics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree Centrality</td>
<td>(-0.408(0.010))</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Efficiency</td>
<td>(-0.361(0.040))</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ParaHippocampal_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal Clustering Coefficient</td>
<td>(-0.367(0.034))</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Local Efficiency</td>
<td>(-0.374(0.027))</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pallidum_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree Centrality</td>
<td>0.424(0.005)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Efficiency</td>
<td>0.445(0.003)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Precentral_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree Centrality</td>
<td>—</td>
<td>0.361(0.040)</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Efficiency</td>
<td>—</td>
<td>0.402(0.012)</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Shortest Path</td>
<td>—</td>
<td>(-0.465(0.001))</td>
<td>—</td>
</tr>
<tr>
<td>Degree Centrality</td>
<td>—</td>
<td>0.395(0.015)</td>
<td>0.388(0.018)</td>
</tr>
<tr>
<td>Postcentral_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal Efficiency</td>
<td>—</td>
<td>0.407(0.010)</td>
<td>0.358(0.043)</td>
</tr>
<tr>
<td>Nodal Shortest Path</td>
<td>—</td>
<td>(-0.410(0.009))</td>
<td>—</td>
</tr>
<tr>
<td>Degree Centrality</td>
<td>—</td>
<td>(-0.378(0.024))</td>
<td>—</td>
</tr>
<tr>
<td>Cerebellum_10_R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betweenness Centrality</td>
<td>—</td>
<td>(-0.377(0.025))</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: ME morningness/eveningness scale, AM amplitude scale, ESS Epworth Sleepiness Scale.

No significant correlation between ESS and brain metrics was found.
Table 4.5: Evening session - partial correlations between global and nodal metrics with ME, AM, and ESS scores ($n = 62$). The significance level is set at $p < 0.05$ and adjusted for the Bonferroni correction.

<table>
<thead>
<tr>
<th></th>
<th>Partial Correlation ($p$ - value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ME</td>
</tr>
<tr>
<td><strong>Global Metrics</strong></td>
<td></td>
</tr>
<tr>
<td>Assortativity</td>
<td>0.429(0.022)</td>
</tr>
<tr>
<td>Average Path Length</td>
<td>0.323(0.042)</td>
</tr>
<tr>
<td><strong>Nodal Metrics</strong></td>
<td></td>
</tr>
<tr>
<td>Hippocampus$_R$</td>
<td></td>
</tr>
<tr>
<td>Nodal Clustering Coefficient</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Local Efficiency</td>
<td>—</td>
</tr>
<tr>
<td>ParaHippocampal$_L$</td>
<td></td>
</tr>
<tr>
<td>Nodal Local Efficiency</td>
<td>—</td>
</tr>
<tr>
<td>Nodal Shortest Path</td>
<td>0.382(0.022)</td>
</tr>
<tr>
<td>Pallidum$_R$</td>
<td></td>
</tr>
<tr>
<td>Degree Centrality</td>
<td>0.353(0.049)</td>
</tr>
</tbody>
</table>

Abbreviations: ME morningness/eveningness scale, AM amplitude scale, ESS Epworth Sleepiness Scale.
Figure 4.2: Area under the curve in the morning session (blue) and the evening session (gray) for degree centrality (A) and betweenness centrality (B) of all 116 brain regions. Significant diurnal fluctuations are represented by red lines.
Figure 4.3: Modular properties of the morning session (A) and the evening (B) session at a sparsity of 0.1 (based on the average connectivity matrix). Node connections within each module are represented in the module’s color, while connections between different modules are represented in gray.
Figure 4.4: The mean connectogram across all participants in both conditions (morning vs. evening) at the thresholding value of 0.1. Abbreviations: SMN sensorimotor network, VN visual network, FPN frontoparietal network, DMN default mode network, LS limbic system, CRB cerebellar network, VMS vermis.
CHAPTER 5: DISCUSSION

In this study, we used rs-fMRI and graph theory to examine diurnal fluctuation of whole-brain connectivity architecture across 62 healthy and young subjects, taking into account their chronotypes. The results of the study revealed meaningful information about the topological alterations of the brain network during the day, as well as the associations of graph theoretical metrics with the variables of interest (e.g., ME, AM, and ESS scores), which are as follows:

(1) Among the global measures, there was a significant increase in both small-worldness and synchroniziation in the evening session compared to the morning session \((p<0.05, \text{ Bonferroni corrected})\), however, there was no compelling evidence of changes in any of the global metrics in terms of chronotype (i.e., between morning- and evening-type participants);

(2) Local graph measures varied (during the day) predominantly across the left hemisphere in areas such as precentral gyrus, putamen, inferior frontal gyrus (orbital part), inferior temporal gyrus, as well as the bilateral cerebellum \((p<0.05, \text{ Bonferroni corrected})\), however, local metrics were mainly consistent with chronotype changes \((p>0.05)\). Moreover, the analysis of the modularity index showed an increase in the number of modules in the evening compared to the morning;

(3) Analysis of the hubs demonstrated that the sensorimotor network was the densest area of the brain (in terms of hubs number) in both morning and evening sessions with mostly provincial type, while hubs in default mode, limbic and cerebellar networks were primarily connector;

(4) Partial correlation analysis revealed significant associations between the variables derived from the questionnaires (such as ME, AM, and ESS) and the nodal characteristics of a number of brain regions in both sessions, most of which were related to morning. For example, the ME score was correlated (positive or negative) with areas such as right hippocampus, right parahippocampus,
and right pallidum in the morning session, while in the evening it was correlated with left parahip-
locampal gyrus and right pallidum. Also, correlations between the AM score and left precentral
and postcentral gyri, as well as right lobule X of cerebellum were evident in the morning session,
although in the evening the correlations were only related to the right hippocampus.

Diurnal Variations in Small-world Property and Network Synchronization

A small-world network is an intermediary between random and regular networks, consisting a
large number of short-range connections alongside a few long-range shortcuts (Watts and Strogatz,
1998). Mathematically, small-world networks have a high clustering coefficient and short average
path length, which makes them superior to other networks in terms of functional segregation (lo-
cal specialization) and integration (global information flow), respectively (Bassett and Bullmore,
2006; Rubinov and Sporns, 2010). According to our rs-fMRI findings, a higher value of small-
worldness in the evening compared to the morning, reflects a more efficient functional topology
and less wiring cost. In another study, Anderson et al. (2017) explored how time-of-day affects
the functional brain networks in older adults across rest and task states. They found no topological
changes at resting-state, although their observations during task were accompanied by a decrease
in small-worldness and modularity in the afternoon (3:00 pm) compared to the morning (8:00 am).

Moreover, a higher amount of network synchronization — a measure for assessing how well all
nodes fluctuate in the same wave pattern — in the evening than in the morning are in line with
the results of Barahona and Pecora (2002), who believed that in networks of low redundancy, the
small-world attitude results in more efficient synchrony than standard deterministic graphs, random
graphs, and ideal constructive schemes. However, while the global effects of circadian rhythms on
the whole-brain connectivity patterns have been examined, relatively little is understood about the
organization of the hypothalamic suprachiasmatic nucleus (SCN), the control center for the body’s
"biological clock" (Abel et al., 2016). The SCN network is believed to be scale-free (Barabási and Albert, 1999; Hafner et al., 2012) and to possess small-world characteristics (Vasalou et al., 2009). In this regard, various studies have reported that the small-world properties of the SCN lead to more precise circadian fluctuations, a larger amplitude, higher synchrony and shifts more rapidly after the emergence of a new light/dark cycle compared to purely random or regular networks (Bodenstein et al., 2012; Gu et al., 2016; Hafner et al., 2012; Šimonka et al., 2015; Vasalou et al., 2009; Webb et al., 2012).

Nodal Changes over the Course of the Day

In this subsection, the results obtained in Table 4.1, which are related to the topological changes of the brain across the day, are described in detail. Our findings here are mainly related to the language center, sensorimotor circuit, and subcortical portions of the limbic system.

Language Processing

Through a morphometric approach, Trefler et al. (2016) discovered considerable effects of time-of-day on the lateral surfaces of the left frontal, temporal, and parietal cortices that are highly associated with the linguistic processing (Chai et al., 2016). In view of temporal lobe, our findings highlight a substantial reduction in neural activity in particular areas of this lobe, including the bilateral inferior, right middle, and left superior temporal gyri, as the waking time increases. Such differences in functional connectivity profile across time-of-day have been previously reported in other studies (Anderson et al., 2014; Fafrowicz et al., 2019; Jiang et al., 2016; Maire et al., 2018), which are in line with our results. Notably, the left superior temporal gyri is the location of Wernicke’s area in about 95% of right-handed individuals and 60% of left-handed individuals.
(Friederici, 2017), which is primarily responsible for speech comprehension and interpreting the visually and auditory perceived words (Hall, 2010).

We also found that the activity of the inferior parietal lobule of the left hemisphere (i.e., the left angular and supramarginal gyri), was substantially affected by time-of-day. This multimodal association area (also known as “Geschwind’s territory”) which lies at the junction of the visual, auditory and somatosensory cortices, is connected by large bundles of nerve fibers to both Broca’s area and Wernicke’s area. This combination of traits makes the inferior parietal lobule an ideal candidate for apprehending the multiple properties of spoken and written words: their sound, their appearance, their function, etc.

Considering the frontal lobe, significant evidence of reduced responses was found in the left inferior frontal gyrus (orbital part) and left superior frontal gyrus (dorsolateral part) across the day, as in previous studies (Jiang et al., 2016; Muto et al., 2016; Vandewalle et al., 2009; Zhu et al., 2019). Importantly, the inferior frontal gyrus holds Broca’s area, which plays a critical role in language and speech production. On the whole, these findings could open up new avenues for understanding the multimodal property of the neurons in the left frontal, temporal, and parietal cortices in production and comprehension of human language, visual memory, as well as labeling things over the course of the day, a prerequisite for concept formation and abstract thinking.

*Cerebellum and Sensorimotor Circuit*

Our results disclosed a decreased functional connectivity throughout the course of the day in some sensorimotor brain areas such as the precentral gyrus (motor region) and supplementary motor area, in agreement with previous studies (Fafrowicz et al., 2019; Tüshaus et al., 2017). However, Wilson et al. (2014) used magnetoencephalography (MEG) to evaluate oscillatory activity during a finger-tapping task, as well as at rest across different times a day, and obtained conflicting results from
our study. Interestingly, Fafrowicz et al. (2019) found an increased functional interaction between the cerebellum and postcentral gyrus across time-of-day, might reflecting more involvement of the sensorimotor network in the morning. Sensorimotor function is a fundamental brain function in humans, and the cerebrocerebellar circuit is essential to this function. Indeed, many resting-state functional connectivity studies have demonstrated that the cerebellum is a member of the sensorimotor network in the adult brain (Buckner et al., 2011; Guell et al., 2018; Kipping et al., 2013).

In this regard, significant diurnal variations were also detected in the cerebellum, especially the cerebral crus which contains the motor tracts. The role of the cerebellum in the context of circadian rhythmicity has rarely been reported. However, studies have shown that the cerebellum, in conjunction with the dorsal striatum (caudate-putamen), serves to regulate the locomotor activity rhythm under restricted feeding, a behavior that is modulated by circadian genes (Mendoza et al., 2010; Verwey and Amir, 2012). The researchers also believe that these two areas are interconnected and contribute collaboratively to motor control (Bostan and Strick, 2010; Middleton and Strick, 2000). In another study, Frederick et al. (2014) simultaneously recorded local field potentials (LFPs) in the striatum and cerebellum. They observed that neural oscillations in these two areas and their synchronization were modulated by time-of-day, and that these variations were affected by dopamine manipulation. Altogether, these findings may provide insight into how cerebellar and sensorimotor alterations are associated with motor activities and other cognitive functions over the course of the day.

**Limbic System**

In the evening compared to the morning, nodal analysis revealed a significant reduction in functional connectivity of the subcortical portions of the limbic system, including the bilateral thalamus
and left putamen. The thalamus is made up of numerous nuclei that each serve a unique role, ranging from relaying sensory and motor signals on the way to the cerebral cortex (Huguenard and McCormick, 2007), as well as regulation of sleep/wake cycle, consciousness and alertness because of the very photic and non-photic inputs into the SCN (Jan et al., 2009). Using rs-fMRI amplitudes of low-frequency fluctuation (also known as ALFF-based FC analysis), Fafrowicz et al. (2019) achieved similar results with our findings on thalamic changes across the day. Considering the effects of chronotype and time-of-day using the n-back paradigm, Schmidt et al. (2015) discovered that higher task complexity results in an increase in thalamic and frontal brain activity, indicating the stability of working memory performance throughout the day.

The putamen — one of the nuclei that compose the basal ganglia — is involved in controlling movements and different types of learning such as reinforcement learning (Yamada et al., 2004) and category learning (Ell et al., 2006). Examining the effects of time-of-day on the brain’s reward circuitry, the researchers found that the left putamen showed relatively less activity in the afternoon (Byrne et al., 2017; Murray et al., 2018), which is consistent with our results.
CHAPTER 6: CONCLUSION

The present findings based on graph-theoretic measures underline the dynamic variations in functional human connectome and show how brain architecture changes during the day. Regional time courses were extracted from each participant during resting state at two different sessions: about 1 hour after the wake-up time (morning) and about 10 hours after the wake-up time (evening). After constructing the corresponding adjacency matrices, the commonly used global and local graph measures were calculated for each subject at each session. We detected that the small-worldness and synchronization were significantly increased throughout the course of the day, reflecting more neuronal efficiency during the evening compared to the morning. Moreover, local graph measures were shifted predominantly across the left hemisphere in areas involved in language processing, sensorimotor control, as well as subcortical portions of the limbic system. However, there was no compelling evidence of changes in any of the global and local metrics in terms of chronotype. Furthermore, we found that the sensorimotor network was the densest area of the brain (in terms of hubs number) in both sessions with mostly provincial type, while hubs in default mode, limbic and cerebellar networks were primarily connector type. Last but not least, substantial associations between the variables derived from the questionnaires (such as ME, AM, and ESS) and the nodal characteristics of a number of brain regions in both sessions such as hippocampus, parahippocampal gyrus, and pallidum, were detected using correlation analysis.

Research Contributions

The major contributions of this study are as follow: (1) application of a graph theoretical approach for modeling the circadian variations in the brain network; (2) investigation of the effects of time of day and chronotype on whole brain functional connectivity, simultaneously; (3) assessment of
both global and local graph theoretic characteristics; and (4) consideration of the areas under the curve (AUC) to provide a scaler that does not depend on a specific threshold selection.

Future Directions

There is a variety of research directions that are worth further investigation. First, by dividing the entire time points to different time windows, one can modeling the time varying brain connectivity using fMRI signals. By doing this, in addition to the previous variables, we can focus on more dynamism in the structure of the brain. Second, researchers can identify the imaging markers of cognitive alterations in a wide range of neurobehavioral events across the time of day from the perspective we used in this study. Third, regardless of the specific application, further studies can be done by utilizing our graph theoretical approach to make neurobiological inferences concerning the mechanisms underlying human cognition, behavior, and different brain disorders. Forth, in view of neuroergonomics area, researchers can assess the human performance under cognitive or physical tasks to model the brain functional network, e.g., they can determine the effects of different levels of exertion on brain topology by employing a physical lifting task.
Table A.1: Summary of each parcellation’s abbreviation, full description, corresponding MNI coordinates, and the associated RGB code in the study.

<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Description</th>
<th>MNI coordinates</th>
<th>RGB code</th>
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<tr>
<td>SENSORIMOTOR NETWORK (SMN)</td>
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<tr>
<td>ROL.L</td>
<td>Left Rolandic operculum</td>
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<td>PoCG.R</td>
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<td>SPG.L</td>
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<td>SMG.L</td>
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<td>VISUAL NETWORK (VN)</td>
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<td>Left calcarine sulcus</td>
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<td>Right calcarine sulcus</td>
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<td>Abbr.</td>
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<td>MNI coordinates</td>
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<td>Left cuneus</td>
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<td>CUN.R</td>
<td>Right cuneus</td>
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<td>LING.L</td>
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<td>LING.R</td>
<td>Right lingual gyrus</td>
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<tr>
<td>SOG.L</td>
<td>Left superior occipital gyrus</td>
<td>-16.54, -84.26, 28.17</td>
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<td>SOG.R</td>
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<td>MOG.L</td>
<td>Left middle occipital gyrus</td>
<td>-32.39, -80.73, 16.11</td>
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<td>MOG.R</td>
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<td>IOG.L</td>
<td>Left inferior occipital cortex</td>
<td>-36.36, -78.29, -7.84</td>
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<tr>
<td>IOG.R</td>
<td>Right inferior occipital cortex</td>
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<td>FFG.L</td>
<td>Left fusiform gyrus</td>
<td>-31.16, -40.3, -20.23</td>
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<td>FFG.R</td>
<td>Right fusiform gyrus</td>
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<tr>
<td>ITG.L</td>
<td>Left inferior temporal gyrus</td>
<td>-49.77, -28.05, -23.17</td>
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<tr>
<td>ITG.R</td>
<td>Right inferior temporal gyrus</td>
<td>53.69, -31.07, -22.32</td>
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**FRONTOPARIETAL NETWORK (FPN)**

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<th>RGB code</th>
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<td>MFG.L</td>
<td>Left middle frontal gyrus</td>
<td>-33.43, 32.73, 35.46</td>
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<tr>
<td>MFG.R</td>
<td>Right middle frontal gyrus</td>
<td>37.59, 33.06, 34.04</td>
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<tr>
<td>ORBmid.L</td>
<td>Left middle frontal gyrus, orbital part</td>
<td>-30.65, 50.43, -9.62</td>
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<tr>
<td>ORBmid.R</td>
<td>Right middle frontal gyrus, orbital part</td>
<td>33.18, 52.59, -10.73</td>
<td>255, 240, 191</td>
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<tr>
<td>IFGoperc.L</td>
<td>Left inferior frontal gyrus, pars opercularis</td>
<td>-48.43, 12.73, 19.02</td>
<td>255, 153, 200</td>
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<td>IFGoperc.R</td>
<td>Right inferior frontal gyrus, pars opercularis</td>
<td>50.2, 14.98, 21.41</td>
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<td>IFGtriang.L</td>
<td>Left inferior frontal gyrus, pars triangularis</td>
<td>-45.58, 29.91, 13.99</td>
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<td>IFGtriang.R</td>
<td>Right inferior frontal gyrus, pars triangularis</td>
<td>50.33, 30.16, 14.17</td>
<td>255, 164, 200</td>
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<tr>
<td>ORBinf.L</td>
<td>Left inferior frontal gyrus, pars orbitalis</td>
<td>-35.98, 30.71, -12.11</td>
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<tr>
<td>ORBinf.R</td>
<td>Right inferior frontal gyrus, pars orbitalis</td>
<td>41.22, 32.23, -11.91</td>
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<tr>
<td>IPL.L</td>
<td>Left inferior parietal lobule</td>
<td>-42.8, -45.82, 46.74</td>
<td>255, 192, 201</td>
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<td>Abbr.</td>
<td>Description</td>
<td>MNI coordinates</td>
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<tr>
<td>IPL.R</td>
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<td>46.46, -46.29, 49.54</td>
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<td>ANG.L</td>
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<td>-44.14, -60.82, 35.59</td>
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<tr>
<td>ANG.R</td>
<td>Right angular gyrus</td>
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<tr>
<td>TPOsup.L</td>
<td>Left superior temporal pole</td>
<td>-39.88, 15.14, -20.18</td>
<td>255, 208, 202</td>
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<tr>
<td>TPOsup.R*</td>
<td>Right superior temporal pole</td>
<td>48.25, 14.75, -16.86</td>
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**DEFAULT MODE NETWORK (DMN)**

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<tr>
<td>PreCG.L</td>
<td>Left precentral gyrus</td>
<td>-38.65, -5.68, 50.94</td>
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<tr>
<td>PreCG.R</td>
<td>Right precentral gyrus</td>
<td>41.37, -8.21, 52.09</td>
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<td>SFGdor.L</td>
<td>Left superior frontal gyrus</td>
<td>-18.45, 34.81, 42.2</td>
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<td>SFGdor.R</td>
<td>Right superior frontal gyrus</td>
<td>21.9, 31.12, 43.82</td>
<td>204, 255, 153</td>
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<tr>
<td>ORBsup.L</td>
<td>Left superior frontal gyrus, orbital part</td>
<td>-16.56, 47.32, -13.31</td>
<td>153, 255, 0</td>
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<tr>
<td>ORBsup.R</td>
<td>Right superior frontal gyrus, orbital part</td>
<td>18.49, 48.1, -14.02</td>
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<td>SFGmed.L</td>
<td>Left medial frontal gyrus</td>
<td>-4.8, 49.17, 30.89</td>
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<td>SFGmed.R</td>
<td>Right medial frontal gyrus</td>
<td>9.1, 50.84, 30.22</td>
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<td>ORBsupmed.L</td>
<td>Left medial orbitofrontal cortex</td>
<td>-5.17, 54.06, -7.4</td>
<td>102, 153, 0</td>
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<tr>
<td>ORBsupmed.R</td>
<td>Right medial orbitofrontal cortex</td>
<td>8.16, 51.67, -7.13</td>
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<td>REC.L</td>
<td>Left gyrus rectus</td>
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<td>Right gyrus rectus</td>
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<td>Left anterior cingulate gyrus</td>
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<td>Right anterior cingulate gyrus</td>
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<td>PCG.L</td>
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<td>PCG.R</td>
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<td><strong>LIMBIC SYSTEM (LS)</strong></td>
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<td>OLF.L</td>
<td>Left olfactory cortex</td>
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<td>HIP.L</td>
<td>Left hippocampus</td>
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<tr>
<td>HIP.R</td>
<td>Right hippocampus</td>
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<td>PHG.L</td>
<td>Left parahippocampal gyrus</td>
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<td>AMYG.L</td>
<td>Left amygdala</td>
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<td>CAU.R</td>
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<td>Right globus pallidus</td>
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<td>THA.L</td>
<td>Left thalamus</td>
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<td>THA.R</td>
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<td>TPOmid.R</td>
<td>Right middle temporal pole</td>
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<td>CRBLCrus1.R</td>
<td>Right crus I of cerebellum</td>
<td>37.46, -67.14, -29.55</td>
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<td>CRBLCrus2.L</td>
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<td>-28.64, -73.26, -38.20</td>
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<td>Right crus II of cerebellum</td>
<td>32.06, -69.02, -39.95</td>
<td>55, 55, 55</td>
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<table>
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<th>Abbr.</th>
<th>Description</th>
<th>MNI coordinates</th>
<th>RGB code</th>
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</thead>
<tbody>
<tr>
<td>CRBL3.L</td>
<td>Left lobule III of cerebellum</td>
<td>-8.80, -37.22, -18.58</td>
<td>80, 80, 80</td>
</tr>
<tr>
<td>CRBL3.R</td>
<td>Right lobule III of cerebellum</td>
<td>12.32, -34.47, -19.39</td>
<td>80, 80, 80</td>
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<tr>
<td>CRBL45.L</td>
<td>Left lobule IV, V of cerebellum</td>
<td>-15.00, -43.49, -16.93</td>
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<td>CRBL45.R</td>
<td>Right lobule IV, V of cerebellum</td>
<td>17.20, -42.86, -18.15</td>
<td>105, 105, 105</td>
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<tr>
<td>CRBL6.L</td>
<td>Left lobule VI of cerebellum</td>
<td>-23.24, -59.10, -22.13</td>
<td>130, 130, 130</td>
</tr>
<tr>
<td>CRBL6.R</td>
<td>Right lobule VI of cerebellum</td>
<td>24.69, -58.32, -23.65</td>
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<tr>
<td>CRBL7b.L</td>
<td>Left lobule VIIB of cerebellum</td>
<td>-32.36, -59.82, -45.45</td>
<td>155, 155, 155</td>
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<td>CRBL7b.R</td>
<td>Right lobule VIIB of cerebellum</td>
<td>33.14, -63.18, -48.46</td>
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<tr>
<td>CRBL8.L</td>
<td>Left lobule VIII of cerebellum</td>
<td>-25.75, -54.52, -47.68</td>
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<tr>
<td>CRBL8.R</td>
<td>Right lobule VIII of cerebellum</td>
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<td>CRBL9.L</td>
<td>Left lobule IX of cerebellum</td>
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<tr>
<td>CRBL9.R</td>
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<td>CRBL10.L</td>
<td>Left lobule X of cerebellum</td>
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<td>CRBL10.R</td>
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<td>Vermis12</td>
<td>Lobule I, II of vermis</td>
<td>0.76, -38.79, -20.05</td>
<td>255, 153, 153</td>
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<td>Vermis3</td>
<td>Lobule III of vermis</td>
<td>1.38, -39.93, -11.40</td>
<td>204, 0, 51</td>
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<tr>
<td>Vermis45</td>
<td>Lobule IV, V of vermis</td>
<td>1.22, -52.36, -6.11</td>
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<td>Vermis6</td>
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<td>Vermis7</td>
<td>Lobule VII of vermis</td>
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<td>Vermis8</td>
<td>Lobule VIII of vermis</td>
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<tr>
<td>Vermis9</td>
<td>Lobule IX of vermis</td>
<td>0.86, -54.87, -34.90</td>
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<tr>
<td>Vermis10</td>
<td>Lobule X of vermis</td>
<td>0.36, -45.80, -31.68</td>
<td>255, 0, 0</td>
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</tbody>
</table>
APPENDIX B: IRB DETERMINATION
Memorandum

To: Farzad Vasheghani-Farahani
From: UCF Institutional Review Board (IRB)
Date: June 3, 2020
Re: Request for IRB Determination

The IRB reviewed the information related to your dissertation Identifying Diurnal Variability of Brain Connectivity Patterns using Graph Theory.

As you know, the IRB cannot provide an official determination letter for your research because it was not submitted into our electronic submission system.

However, if you had completed a Huron submission, the IRB could make one of the following research determinations: “Not Human Subjects Research,” “Exempt,” “Expedited” or “Full Board.

Based on the information you provided, this study would have been issued a Not Human Subjects Research determination outcome letter had a request for a formal determination been submitted to the UCF IRB through Huron IRB system.

If you have any questions, please contact the UCF IRB irb@ucf.edu.

Sincerely,

Renee Carver
IRB Manager
LIST OF REFERENCES
LIST OF REFERENCES


Farahani, F. V., Fafrowicz, M., Karwowski, W., Douglas, P., Domagalik, A., Beldzik, E., Oginska, H., and


