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The Effects of Chronic Sleep Deprivation on Sustained Attention: A Study of Brain Dynamic Functional Connectivity

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THE EFFECTS OF CHRONIC SLEEP DEPRIVATION ON SUSTAINED ATTENTION: A STUDY OF BRAIN DYNAMIC FUNCTIONAL CONNECTIVITY

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ABSTRACT

It is estimated that about 35-40% of adults in the U.S. suffer from insufficient sleep. Chronic sleep deprivation has become a prevalent phenomenon because of contemporary lifestyle and work-related factors. Sleep deprivation can reduce the capabilities and efficiency of attentional performance by impairing perception, increasing effort to maintain concentration, as well as introducing vision disturbance. Thus, it is important to understand the neural mechanisms behind how chronic sleep deprivation impairs sustained attention.

In recent years, more attention has been paid to the study of the integration between anatomically distributed and functionally connected brain regions. Functional connectivity has been widely used to characterize brain functional integration, which measures the statistical dependency between neurophysiological events of the human brain. Further, evidence from recent studies has shown the non-stationary nature of brain functional connectivity, which may reveal more information about the human brain. Thus, the objective of this thesis is to investigate the effects of chronic sleep deprivation on sustained attention from the perspective of dynamic functional connectivity.

A modified spatial cueing paradigm was used to assess human sustained attention in rested wakefulness and chronic sleep deprivation conditions. Partial least squares approach was applied to distinguish brain functional connectivity for the experimental conditions. With the integration of a sliding-window approach, dynamic patterns of brain functional connectivity were identified in two experimental conditions. The brain was modeled as a series of dynamic functional networks in each experimental condition. Graph theoretic analysis was performed to

investigate the dynamic properties of brain functional networks, using network measures of clustering coefficient and characteristics path length.

In the chronic sleep deprivation condition, a compensation mechanism between highly clustered organization and ineffective adaptability of brain functional networks was observed. Specifically, a highly clustered organization of brain functional networks was illustrated with a large clustering coefficient. This organization suggested that brain utilizes more connections to maintain attention in the chronic sleep deprivation condition. A smaller impact of clustering coefficient variation on characteristics path lengths indicated an ineffective adaptability of brain functional networks in the chronic sleep deprivation condition.

In the rested wakefulness condition, brain functional networks showed the small-world topology in general, with the average small-world topology index larger than one. Small-world topology was identified as an optimal network structure with the balance between local information processing and global integration. Given the fluctuating values of the index over time, small-world brain networks were observed in most cases, indicating an effective adaptability of the human brain to maintain the dominance of small-world networks in the rested wakefulness condition. On the contrary, given that the average small-world topology index was smaller than one, brain functional networks generally exhibited random network structure. From the perspective of dynamic functional networks, even though there were few cases showing small-world brain networks, brain functional networks failed to maintain the dominance of small-world topology in the chronic sleep deprivation condition.

In conclusion, to the best of our knowledge this thesis was the first to investigate the effects of chronic sleep deprivation on sustained attention from the perspective of dynamic brain functional connectivity. A compensation mechanism between highly clustered organization and

ineffective adaptability of brain functional networks was observed in the chronic sleep deprivation condition. Furthermore, chronic sleep deprivation impaired sustained attention by reducing the effectiveness of brain functional networks' adaptability, resulting in the disrupted dominance of small-world brain networks.

TABLE OF CONTENTS

LIST OF FIGURES x

LIST OF TABLES xii

LIST OF ACRONYMS xiii

CHAPTER 1: INTRODUCTION 1

CHAPTER 2: LITERATURE REVIEW 3

2.1 Total vs. Chronic Sleep Deprivation 3

2.2 Impairments of Sustained Attention in the sleep deprivation condition 4

2.3 Neural Basics of Attention and Attentional Control 5

2.3.1 Attention 5

2.3.2 Attentional Control 8

2.4 Brain Functional Connectivity 9

2.4.1 Functional Connectivity 10

2.4.2 Dynamic Functional Connectivity 11

2.5 Graph Theoretic Analysis in Human Brain Networks 12

2.5.1 Construction of Brain Networks 13

2.5.2 Network Measures in Brain Network 14

2.5.3 Topology of Brain Networks 15

CHAPTER 3: RESEARCH GAPS AND OBJECTIVE 18

CHAPTER 4: RESEARCH EXPERIMENT AND DATA 20

4.1 Participants 20
4.2 Experiment Protocol 20
4.3 Tasks 21
4.4 Eye-tracking data collection and preprocessing 23
4.5 fMRI data collection and preprocessing 24
CHAPTER 5: METHODOLOGY 25
5.1 Automated Anatomical Labeling 26
5.2 Sliding-Window Pearson Correlation Coefficient 31
5.3 Partial Least Squares Approach 33
    5.3.1 Notation 33
    5.3.2 Data Organization 34
    5.3.3 Singular Value Decomposition 38
    5.3.4 Brain Functional Connectivity Estimation 40
5.4 Construction of Brain Dynamic Functional Networks 41
5.5 Graph Theoretic Analysis 41
    5.5.1 Clustering Coefficient 42
    5.5.2 Characteristic Path Length 43
5.6 Small-World Topology of Brain Functional Networks 43
CHAPTER 6: RESULTS 45
6.1 Performance Analysis 45
6.2 Estimated Brain Dynamic Functional Connectivity 46
6.3 Graph Theoretic Analysis 50

6.3.1 Clustering Coefficient of Brain Functional Networks 50

6.3.2 Characteristic Path Lengths of Brain Functional Networks 51

6.4 Small-World Topology of Brain Functional Networks 52

6.4.1 Small-World Topology Index in the rested wakefulness condition................. 52

6.4.2 Small-World Topology Index in the chronic sleep deprivation condition 55

CHAPTER 7: DISCUSSION 58

7.1 Dynamic Patterns of Brain Functional Connectivity 58

7.2 Graph Theoretic Analysis of Brain Dynamic Functional Networks............................. 60

7.3 Dynamic Topology of Brain Functional Networks 62

7.4 Impaired Sustained Attention in the chronic sleep deprivation condition.................... 64

CHAPTER 8: CONCLUSION 67

LIST OF REFERENCES 70

LIST OF FIGURES

Figure 1. Representation of Three Types of Network Topology with Associated Network Measures (Guye et al., 2010) 16
Figure 2. Illustration of Congruent Task 22
Figure 3. Illustration of Incongruent Task 22
Figure 4. Eye Tracking System (Fafrowicz et al., 2010) 24
Figure 5. Illustration of Listed Brain Regions in the Frontal Lobe 28
Figure 6. Illustration of Listed Brain Regions in the Parietal Lobe 28
Figure 7. Illustration of Listed Brain Regions in the Occipital Lobe 29
Figure 8. Illustration of Listed Brain Regions in the Central Region 29
Figure 9. An Example of Estimating Regional Activation after AAL Segmentation 30
Figure 10. An Example of Calculating Pearson Correlation Coefficient 31
Figure 11. Sliding-Window Pearson Correlation Coefficient 32
Figure 12. Design Matrix (**Y**) of Partial Least Squares Approach 34
Figure 13. Illustration of Constructing Individual Connectivity Matrix with Sliding-Window Correlation Matrix 35
Figure 14. Illustration of Constructing Brain Connectivity Matrix (**X**) with Individual Connectivity Matrices 36
Figure 15. Data Organization of Brain Connectivity Matrix (**X**) 37
Figure 16. Example of Relating Connectivity to Experimental Condition through Design Scores 39
Figure 17. Illustration of Partial Least Squares Approach Outputs 47

Figure 18. Estimated Dynamic Functional Connectivity 47

Figure 19. Example of Estimated Functional Connectivity Pair 39 48

Figure 20. Three Examples of Dynamic Functional Connectivity in Brain Atlas 49

Figure 21. The Average Clustering Coefficients of Brain Functional Networks 51

Figure 22. Characteristic Path Lengths of Brain Functional Networks 52

Figure 23. Clustering Coefficients of Brain Functional Networks and Similar Random Networks in the rested wakefulness condition 53

Figure 24. Characteristic Path Lengths of Brain Functional Networks and Similar Random Networks in the rested wakefulness condition 54

Figure 25. Values of Small-World Topology Index in the rested wakefulness condition 55

Figure 26. Clustering Coefficients of Brain Functional Networks and Similar Random Networks in the chronic sleep deprivation condition 56

Figure 27. Characteristic Path Lengths of Brain Functional Networks and Similar Random Networks in the chronic sleep deprivation condition 57

Figure 28. Values of Small-World Topology Index in the chronic sleep deprivation condition.. 57

LIST OF TABLES

Table 1. List of AAL Brain Regions 27

Table 2. ANOVA Results of Sustained Attention Performance 45

LIST OF ACRONYMS

AAL	Anatomical Automated Labeling
ACN	Anti-correlated Network
AD	Alzheimer’s Disease
ADHD	Attention-Deficit/Hyperactivity Disorder
BOLD	Blood-oxygen-level Dependent
DMN	Default Mode Network
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imaging
LV	Latent Variable
PET	Positron Emission Tomography
PCA	Principal Component Analysis
PLS	Partial Least Squares
RW	Rested Wakefulness Condition
SD	Sleep Deprivation Condition
SVD	Singular Value Decomposition

CHAPTER 1: INTRODUCTION

Sleep has been identified as an adaption of dormancy that benefits human cognition in terms of insight formation (Wagner et al., 2004), novel-language perception (Fenn et al., 2003), visual discrimination (Stickgold et al., 2000), memory consolidation (Walker et al., 2003), and motor skills (Walker et al., 2002). Similarly, studies have demonstrated that sufficient sleep would ensure comprehensive levels of arousal, attention (Lim & Dinges, 2008), cognitive performance (Durmer & Dinges, 2005) and neurobehavioral effectiveness (Banks & Dinges, 2007), and help to avoid potentially adverse health outcomes (Buxton et al., 2012).

Cognitive studies have suggested that adults require around eight to nine hours of sleep in order to maintain normal brain function during the day (Van Dongen et al., 2003). However, according to a survey, about 35-40% of adults in the U.S. obtains less than seven hours of sleep on weekday nights (Basner et al., 2007). Contemporary lifestyle and work-related factors are responsible for the prevalence of sleep deprivation, which lowers the capacity for and efficiency of attention by impairing perception, increasing effort needed to concentrate, as well as introducing visual disturbance (Orzeł-Gryglewska, 2010). For example, sleep deprivation has been found as a vital factor behind accidents for those occupations requiring continuous attention, including truck drivers, air traffic controllers, and health care providers (Jung et al., 2011; Rosekind, 2005).

Drowsy driving following sleep deprivation has been identified as an important factor in most vehicle accidents (Connor et al., 2001). Recent surveys further reveals that the number of road accidents is significantly influenced by the sleep duration and quality of drivers (Stutts et al., 2003). These sleep deprivation related accidents may result from falling asleep while driving

(Carskadon, 1990; Knipling & Wang, 1994; Pack et al., 1995), impaired ability to assess a situation (Kahn-Greene et al., 2006; Muzur et al., 2002), and risky behavior such as inattention to increase driving speed (Peters et al., 1999). In addition, the neurobehavioral impairments following sleep deprivation have been also observed in intoxicated individuals (Arnedt et al., 2001; Dawson & Reid, 1997; Dinges & Kribbs, 1991; Fletcher et al., 2003; Lamond & Dawson, 1999; Maruff et al., 2005; Williamson & Feyer, 2000). However, there are no legal restrictions for sleep deprived drivers, who may also pose a potential hazard to other traffic participants (Orzeł-Gryglewska, 2010).

Health care providers have been identified as a typical occupation that requires high standard of performance, but also suffers habitually from chronic sleep deprivation. Landrigan et al. (2004) have demonstrated that health care residents with a "traditional schedule" make 36% more serious medical errors than those under an "intervention schedule". On the other side, increased muscle tonus has been observed as a compensatory effect for the decreased attention following sleep deprivation (Wilkinson, 1962). The increased tonus will dramatically impact task performance, especially for surgeons that require continuously accurate movements (Arihara & Sakamoto, 1999; Morrison et al., 2005).

Given the negative consequences of sleep deprivation, it is important to understand how sleep deprivation impairs human cognition. Previous studies have provided various evidence of impaired sustained attention following sleep deprivation. However, the neural basis of such impairment has not been clearly understood. Thus, this thesis aims to investigate the effects of chronic sleep deprivation on sustained attention as manifested by brain dynamics.

CHAPTER 2: LITERATURE REVIEW

Previous studies about the effects of sleep deprivation on both human cognitive performance and brain activity are demonstrated in this section. Chronic sleep deprivation has exhibited different effects on human cognition when compared with total sleep deprivation. Impaired sustained attention has been observed in the sleep deprivation condition. The neural mechanism behind attention and attentional control is discussed as well. Brain functional integration is then introduced with the concept of functional connectivity. A graph theoretic analysis is discussed to investigate the property of brain functional networks.

2.1 Total vs. Chronic Sleep Deprivation

The first published study about the effects of sleep deprivation on human cognitive performance was conducted by Patrick and Gilbert (1896). Three adults experienced 90 hours of sustained wakefulness in this study (Patrick & Gilbert, 1896). Impaired cognitions were observed in the sleep deprivation condition, including attention span and memory (Patrick & Gilbert, 1896).

There are three types of studies widely discussed in this area: 1) long-term total sleep deprivation (>45 hours); 2) short-term total sleep deprivation (≤45 hours); and 3) chronic sleep deprivation (<7 hours/24hours) (Durmer & Dinges, 2005). Although it has been demonstrated that total sleep deprivation and chronic sleep deprivation have similar impairments of behavioral and neurocognitive performance (Philip et al., 2012), studies have shown that chronically sleep-deprived subjects require more time for full recovery than those in total sleep deprivation (Cao & Guilleminault, 2012). This may result from long-term neuron modulatory changes in brain physiology, induced by chronic sleep deprivation (Basner et al., 2013). In the chronic sleep deprivation condition, studies have observed a linear relationship between the impaired alerting and the number of days with insufficient sleep (Belenky et al., 2003; Van Dongen et al., 2003).

2.2 Impairments of Sustained Attention in the sleep deprivation condition

Sustained attention has been identified as a cognitive function sensitive to sleep loss (Durmer & Dinges, 2005; Graw et al., 2001; Jewett et al., 1999; Sadeh et al., 2011). Studies about sustained attention have demonstrated that sleep deprivation lowers the capacity for and efficiency of attentional performance by impairing perception, increasing effort needed to maintain concentration, and introducing visual disturbance (Orzeł-Gryglewska, 2010).

Behavioral studies have shown impaired performance during sustained attention tasks in both children and adults following sleep deprivation (Dinges et al., 1997; Peters et al., 2009; Sadeh et al., 2002; Van Dongen et al., 2003; Weaver, 2001). Among these studies, reaction time tasks (e.g., psychomotor vigilance task) have been widely used to assess the psychological processes of attention (Jung et al., 2011). Yerkes (1904) has defined reaction time (or response time, RT) as the time between the brain reacting to a sensory stimuli and make a motor response. Attentional lapse has been defined as a response error with slow response times, usually longer than 500ms (Weissman et al., 2006).

In general, sleep deprived subjects have shown slow response times (i.e., mean RTs, media RTs, reciprocal RTs, slowest 10% of RTs, and fastest 10% of RTs), increased number of attentional lapses, and larger variance of response times (Beaumont et al., 2001; Dinges & Powell, 1989; Doran et al., 2001; Jung et al., 2011; Kjellberg, 1977; Lim & Dinges, 2008;

Pilcher & Huffcutt, 1996; Williams et al., 1959). Specifically, the slowest 10% of RTs has been measured as response times in the lapses domain; and researchers have described the fastest 10% of RTs as the optimum response time (Jung et al., 2011). Large variance of response times has revealed the instability of attentional state in the sleep deprivation condition (Jung et al., 2011).

2.3 Neural Basics of Attention and Attentional Control

The emergence of neuroimaging techniques has enabled researchers to study the neural activity of the human brain. Functional magnetic resonance imaging (fMRI) measures brain activity through identifying associated changes of blood-oxygen-level-dependent (BOLD) contrast. This technique has been widely used to investigate the neural basics of attention and attention control.

2.3.1 Attention

Attention is defined as a cognitive process of selecting relevant information from environments and ignoring the irrelevant (Broadbent, 1958; Desimone & Duncan, 1995; Neisser, 1967; Treisman, 1960). Two types of attention have been widely discussed: endogenous attention and exogenous attention (Purves et al., 2008). Specifically, endogenous attention is the ability to voluntarily allocate attention to certain features, objects, or regions in space depending on one’s goals, expectations, and/or knowledge (Purves et al., 2008; Spreng & Schacter, 2012). In contrast, stimuli arising from the environment attracts attention automatically, which is called exogenous attention (Purves et al., 2008). During exogenous attention tasks, subjects are asked to respond to sensory stimuli directly (Corbetta & Shulman, 2002).

Attention has been conceptualized as an organization made up of three separate functional systems: alerting, orienting, and executive control (Posner & Petersen, 1989). Alerting subsumes the capability to achieve and maintain a general state of activation in the cognitive system (Martella et al., 2011). This function enables the capacity to increase attention to an approaching stimulus, by changing the internal state to perceive the stimulus (Fan et al., 2009). The alerting function has been associated with the thalamic, parietal, and frontal brain regions (Chee & Tan, 2010; Chee et al., 2008; Drummond et al., 2005a; Tomasi et al., 2009); and it can be influenced by the brain's norepinephrine system that emergents from the midbrain nucleus locus coeruleus (Coull et al., 1996; Marrocco et al., 1994). Sleep deprivation has also been characterized as a powerful way of reducing alertness (Killgore, 2010; Lim & Dinges, 2008).

The orienting function selectively allocates attentional focus to the specific information among numerous sensory inputs (Fan & Posner, 2004; Martella et al., 2011). The orienting function for visual events has been associated with the superior and inferior parietal lobule, frontal eye field, and subcortical areas such as the superior colliculus of the midbrain and the pulvinar and the reticular nucleus of the thalamus (Corbetta et al., 2000; Corbetta & Shulman, 2002; Posner et al., 1982; Posner, 1980; Posner & Cohen, 1984).

The effects of sleep loss on attentional orienting are still not clear, with conflicting results (Bocca & Denise, 2006; Casagrande et al., 2006; Martella et al., 2011; Trujillo et al., 2009; Versace et al., 2006). Specifically, researchers found no significant effects on attentional orienting after 24 hours of sustained wakefulness, but general decrease in alertness (Casagrande et al., 2006). In contrast, Versace et al. (2006) suggested the impaired reorienting mechanism in a partial sleep restriction condition.

Executive control is described as the ability of behavioral control to achieve intended goals through resolving conflicts among alternative responses (Martella et al., 2011). This function involves more complex mental operations, and has been most needed in decision making or planning tasks (Fan & Posner, 2004). This function has been associated with the anterior cingulate cortex and lateral prefrontal cortex (Benes, 2000; Matsumoto & Tanaka, 2004).

Studies about the effects of sleep deprivation on higher executive functions have also revealed inconsistent results (Killgore, 2010). For instance, Stenuit and Kerkhofs (2008) have reported a diminished orienting performance following sleep deprivation; however, different studies have failed to confirm this observation. Furthermore, researchers have demonstrated conflicting results about the effects of sleep deprivation on executive control, even using the same tasks (Hsieh et al., 2007; Martella et al., 2011; Murphy et al., 2006; Tsai et al., 2005). These inconsistent results could be attributed to the high inter-subject variability of the effects of sleep deprivation (Banks & Dinges, 2007; Van Dongen et al., 2004).

In addition, studies have early found the reduced metabolic rate in the distributed cortico-thalamic network (i.e., thalamic, parietal, and prefrontal regions) using positron emission tomography (PET).This network has been observed to mediate attention and other high-order cognitive processes during prolonged sleep loss (Thomas et al., 2000; Thomas et al., 2003). This observation has been supported by fMRI studies (Poudel et al., 2010; Tomasi et al., 2009).

2.3.2 Attentional Control

The most prevalent model of attentional control was proposed by Corbetta and Shulman (2002), especially for visual attention control. Attention is controlled by two partially segregated neural systems: top-down control and bottom-up control (Corbetta & Shulman, 2002). These two systems carry out different functions but interact extensively to support attentional control.

The top-down control system is associated with preparing and applying selections of goal-directed sensory stimuli and responses (Corbetta & Shulman, 2002; Purves et al., 2008); in other words, this control system mainly focuses on endogenous attention. This system is associated with parts of the intraparietal cortex and superior frontal cortex (Purves et al., 2008). In the sleep deprivation condition, studies have shown a loss of top-down attention control with attenuated functional connectivity between regions of the parietal lobe and parahippocampal region (Chee & Tan, 2010; Lim et al., 2010). On the other hand, attentional lapses have been related to decreased thalamic activation and attenuated fronto-parietal activation (Chee et al., 2008; Tucker et al., 2011). These observations may reveal a break-down in top-down attentional control following sleep deprivation(De Havas et al., 2012).

The bottom-up control system specializes in detecting behaviorally relevant sensory events, particularly for salience and unattended stimuli (Corbetta & Shulman, 2002; Purves et al., 2008). This system is also referred to as stimulus-driven control, consisting of the temporoparietal and ventral frontal cortex, mainly on the right hemisphere of the brain (Corbetta & Shulman, 2002).

2.4 Brain Functional Connectivity

Most of the functional magnetic resonance imaging studies have focused on the altered brain response to cognitive tasks following sleep deprivation (Chee & Choo, 2004; Drummond & Brown, 2001; Drummond et al., 2000; Drummond et al., 1999; Portas et al., 1998; Poudel et al., 2013). For instance, Poudel et al. (2010) observed decreased activity in the occipital cortex, superior parietal cortex, and primary motor areas during a visuomotor tracking task in the chronic sleep deprivation condition; meanwhile, increased activity in the thalamic, anterior cingulate, and medial frontal areas have been reported. The first fronto-parietal network has been linked with the ability to maintain sustained attention (Corbetta & Shulman, 2002); and the latter thalamo-cortical network has been related to arousal (Sturm et al., 1999).

These studies have assumed that the anatomically segregated cortical regions can be attributed to specific cognitive functions, in terms of brain functional segregation (Friston, 2011). However, researchers have realized that it is difficult to localize a specific function to cortical areas, because of the interdependent cerebral activity among brain regions (Phillips et al., 1984). According to functional segregation, a specific function is localized with anatomically segregated cortical areas (Friston, 2011). However, the union of these cortical areas may be mediated through the functional integration among these areas (Friston, 2011). In this way, Friston (2011) has demonstrated that functional segregation can be meaningful only in terms of functional integration, since a single function may result from the integration of multiple cortical areas. In recent years, the emphasis of researches has been shifting from functional segregation to the integration of the anatomically distributed but functionally connected brain regions (Friston, 2011; Lynall et al., 2010).

2.4.1 Functional Connectivity

Functional connectivity has been widely used to characterize brain functional integration, which measures the statistical dependencies among neurophysiological events of the human brain (Friston, 2011). This concept is based on the assumption that statistical dependencies between time series of neuronal or metabolic activity represent the functional interaction between brain regions (Stam & Reijneveld, 2007). With fMRI data, functional connectivity is calculated as the correlation coefficient between BOLD signals of brain regions acquired during tasks or in the resting state (Park & Friston, 2013). Even the underlying brain anatomical structure may restrict the patterns of functional connectivity; such dependency measures may reveal more information beyond the anatomical structure of the brain (Stam & Reijneveld, 2007).

Researchers have observed two brain instinct networks with functional connectivity, the default mode network (DMN) and its anti-correlated network (ACN). The default mode network has been described as a brain functional network that consistently deactivates when tasks require external orientation (Raichle et al., 2001; Shulman et al., 1997), and activates when tasks involve in internal orientation (Bar, 2007; Binder et al., 2009; D'Argembeau et al., 2005; Hassabis & Maguire, 2007). This network is mainly associated with brain regions, including the posterior cingulate cortex and retrosplenial cortex, precuneus, the dorsal and ventral medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex, and hippocampal formation (Buckner et al., 2008; Fox et al., 2005; Gusnard et al., 2001; Raichle & Snyder, 2007; Shulman et al., 1997).

The anti-correlated network shows activation in response to externally oriented tasks (Andrews-Hanna, 2012; Corbetta & Shulman, 2002; Fox et al., 2005). This network composes such brain regions as the frontal eye filed, intraparietal sulcus, middle temporal region, supplementary motor area , inferior parietal lobe (also referred to as the temporoparietal junction (Corbetta & Shulman, 2002)), dorsolateral prefrontal cortex, and Insula (Fox et al., 2005). In addition, these two brain networks are also mediated through functional connectivity (Greicius et al., 2003).

Studies have observed both altered regional activation and functional connectivity of the default mode network and the anti-correlated network in the human brain after sleep loss (De Havas et al., 2012; Gujar et al., 2010; Sämann et al., 2010). Specifically, task-induced deactivation in brain regions of the default mode network (e.g., midline anterior and posterior) has been observed after one night of sleep loss (Gujar et al., 2010). Researchers have demonstrated that sleep deprivation is associated with the decline of functional connectivity in the default mode network and its anti-correlated network, as well as the functional connectivity between these two networks (De Havas et al., 2012; Sämann et al., 2010).

2.4.2 Dynamic Functional Connectivity

Most of the fMRI studies have assumed that the functional connectivity was constant over time during task-free experiments, which provided a convenient way to examine and interpret results (Hutchison et al., 2013a). However, researchers have argued that this assumption may oversimplify the assessment of brain activity (Allen et al., 2014). Recent work on both task-induced and resting-state brain activity has shown the fluctuated functional connectivity, suggesting a non-stationary property of brain functional connectivity (Handwerker et al., 2012; Hutchison et al., 2013b; Kang et al., 2011; Kiviniemi et al., 2011; Li et al., 2014; Majeed et al., 2011). Specifically, Hutchison et al. (2013a) have demonstrated that functional connectivity was varying over time due to task demands (Esposito et al., 2006; Fornito et al., 2012; Fransson, 2006; Sun et al., 2007), learning (Albert et al., 2009; Bassett et al., 2011; Lewis et al., 2009; Tambini et al., 2010), and state transitions such as sleep (Horovitz et al., 2009; Horovitz et al., 2008). Furthermore, the dynamics of functional connectivity have revealed the time-varying property of both connectivity strength and directionality (Chang & Glover, 2010; Hutchison et al., 2013c; Kiviniemi et al., 2011). Such time-varying property may show greater information about the fundamental properties of brain functional networks (Friston, 2011; Hutchison et al., 2013a).

2.5 Graph Theoretic Analysis in Human Brain Networks

Given that functional connectivity assesses the relationship between brain regions, the human brain can be represented as an interconnected network, which is referred to as brain functional network in the literature (Rubinov & Sporns, 2010). In brain functional networks, nodes represent the brain regions and edges represent the functional connectivity (Lynall et al., 2010; Ma et al., 2014). Given the complexity of the human brain, researchers have applied graph theoretic analysis to brain functional networks, which has been widely used in complex network analysis (Rubinov & Sporns, 2010). The first attempt to apply graph theoretic analysis to fMRI was published by Dodel et al. (2002). Increasing number of studies have investigated brain network properties using graph theoretic analysis (Bassett & Bullmore, 2006; Bassett & Bullmore, 2009; Bullmore & Sporns, 2009; Fallani et al., 2014; Park & Friston, 2013; Rubinov & Sporns, 2010; Stam et al., 2007b). This analysis can reliably to characterized brain functional networks, whose measures are easy to compute and interpret (Achard et al., 2006; Bassett & Bullmore, 2006; Hagmann et al., 2008; He et al., 2007; Sporns & Zwi, 2004).

2.5.1 Construction of Brain Networks

In graph theory, a complex system is represented with a collection of defined nodes interacting with each other through connected edges. Given the large-scale brain networks, the nodes usually represent brain regions, and the edges may represent the anatomical, functional, or effective connections (Friston, 1994). The nodes and edges in different brain networks are determined by the integration of brain mapping methods, anatomical parcellation methods, and measures of connectivity (Rubinov & Sporns, 2010). Nodes represent brain regions composed of neural elements that are connected with extrinsic anatomical or functional connections (Bassett & Bullmore, 2009).

There are four types of edges determined by their weight measures and directionality: binary directed, binary undirected, weighted directed and weighted undirected. Binary edges show the presence or absence of connections. The weights of weighted edges describe the strengths of corresponding connections, which are determined by the measures of connectivity. Directed edges are mainly used with measures of effective connectivity. Binary undirected brain networks are the most widely used because of their simplicity (Rubinov & Sporns, 2010). However, researchers have demonstrated that the weighted edges may reveal somewhat different and complementary aspects of brain networks (Saramäki et al., 2007).

2.5.2 Network Measures in Brain Network

Network measures have been widely used in previous studies, including degree distribution, clustering coefficient, and characteristic path lengths (Rubinov & Sporns, 2010; Tijms et al., 2013; Watts & Strogatz, 1998).

Degree distribution is the most basic and important measure among those network measures. Degree is calculated as the number of neighbors of that node. In weighted networks, a variant of the degree, named as strengths or weighted degree, is defined as the sum of all neighbors' edge weights. The degree distribution is composed of the degrees of all nodes in the network. Such a measure has been widely used to assess network development and resilience. The shape of degree distributions may characterize the brain networks. For instance, in the random networks all nodes are connected with equal probability, resulting in a systematically centered Gaussian distribution (Bullmore & Sporns, 2009). In the scale-free networks, the degree distributions follow a power law distribution, which has been related to the network's robustness to failure. The scale-free networks have also been observed in the human brain (Achard et al., 2006; Eguiluz et al., 2005; Stam & de Bruin, 2004; Stam & Reijneveld, 2007; van den Heuvel et al., 2008).

Clustering coefficient has been widely used as a measure of functional segregation in brain networks. It is calculated as the ratio of the number of connections between the nearest neighbors of a node over the maximum number of possible connections in the network (Watts & Strogatz, 1998). Functional segregation shows the brain's ability of specializing information processing (Rubinov & Sporns, 2010). Given the definition of clustering coefficient, the average clustering coefficient of a network represents the prevalence of clusters in the network. In brain functional networks, the appearance of clusters suggests an organization of segregated neural processing(Rubinov & Sporns, 2010).

Characteristic path length has been widely used as a measure of functional integration in brain networks (Watts & Strogatz, 1998). It is defined as the average shortest path length between all pairs of nodes in the network. Measures of functional integration assess the ease of communication between distinct regions through the functional connectivity (Rubinov & Sporns, 2010). Characteristic path length is also related to another measure, known as the global efficiency, which is equal to the average inverse shortest path length between all pairs of nodes (Latora & Marchiori, 2001; Rubinov & Sporns, 2010).

2.5.3 Topology of Brain Networks

Studying the topology of interactions in brain networks suggests a comprehensive understanding of the complex phenomena, such as the emergence of cognition or disabled functions with brain lesions (Carter et al., 2012; Fallani et al., 2014; Varela et al., 2001). Researchers have linked topology changes of brain structural or functional networks to neurological and psychiatric disorders (Bassett et al., 2008; Leistedt et al., 2009; Ponten et al., 2009; Stam et al., 2007a; Stam et al., 2009; Stam et al., 2007b; Wang et al., 2009).

Three types of network topology have been widely discussed in previous studies (Figure 1), including regular network, small-world network, and random network (Guye et al., 2010). Specifically, the regular network has many short distance connections but no long distance ones, resulting in a high clustering coefficient (C), and a long characteristic path length (L). Network of such topology has the maximal information segregation (Guye et al., 2010; Tijms et al., 2013).

In contrast, the random network shows a low clustering coefficient and a short characteristic path length, since each node has the same probability of connecting with the others. Thus, the random network shows the property of the maximal information integration (Guye et al., 2010; Tijms et al., 2013). By introducing few long distance connections, the regular network is changed to small-world network with a similar clustering coefficient, but a much shorter characteristic path length. Hence, the small-world topology is an intermediate topology between the regular network and the random network. As a result, the network of small-world topology shows an optimal balance between information segregation and integration (Guye et al., 2010; Tijms et al., 2013).

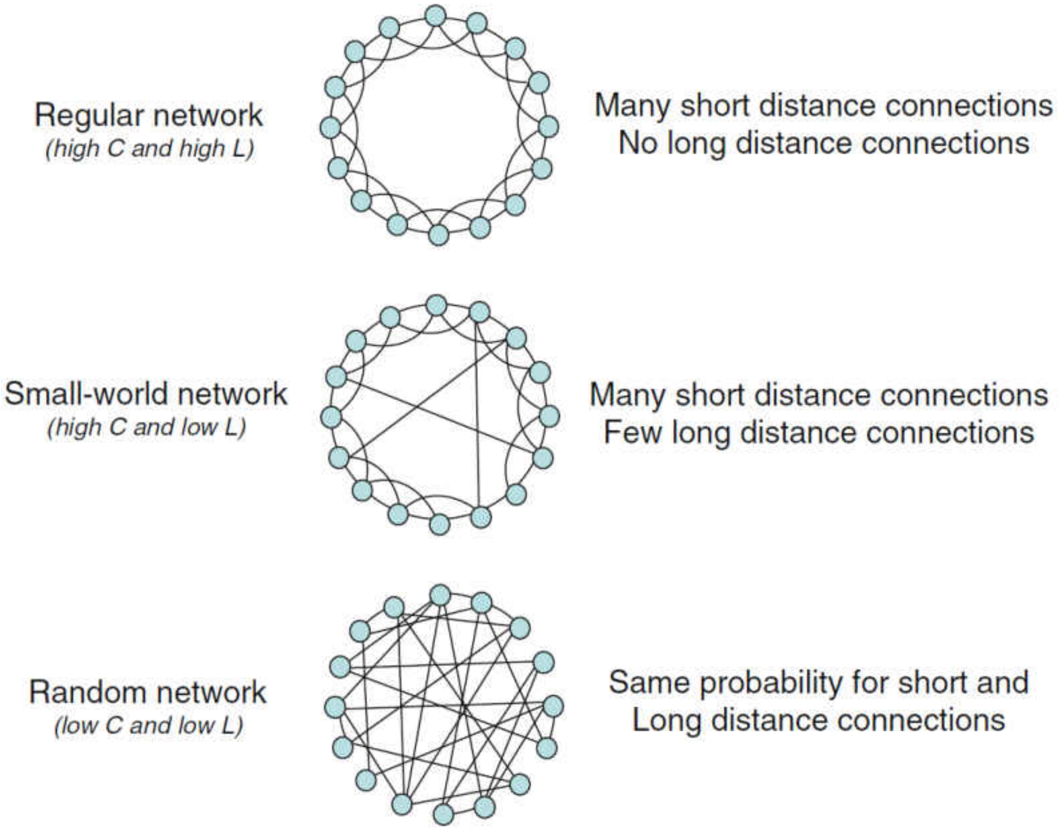


Figure 1. Representation of Three Types of Network Topology with Associated Network Measures (Guye et al., 2010)

Recent studies have demonstrated that brain network intrinsically shows a small-world topology, which is responsible for high efficient information integration with a low cost of reconnecting (Bassett et al., 2009; Guye et al., 2010; Hsu et al., 2012; Latora & Marchiori, 2001; Lynall et al., 2010). Watts and Strogatz (1998) developed the first mathematical model of small-world topology. This topology has been described as an optimal network structure associated with a balance between the information processing and global synchronization (Stam, 2004).

Alterations in small-world topology of brain networks have been related to declining states of consciousness (Salvador et al., 2005), schizophrenia (Micheloyannis et al., 2006; Rubinov et al., 2009), Alzheimer's disease (He et al., 2008; Sanz-Arigita et al., 2010; Stam et al., 2007a; Stam et al., 2009; Stam et al., 2007b), and other cognitive disorders induced by aging (Achard & Bullmore, 2007; Meunier et al., 2009). In addition, Koenis et al. (2013) have reported the loss of brain small-world networks with electroencephalogram (EEG) data in the sleep deprivation condition. However, Liu et al. (2014) have demonstrated that sleep deprivation resulted in an enhanced brain small-worldness with resting state fMRI data, indicating a compensatory adaptation of the human brain.

CHAPTER 3: RESEARCH GAPS AND OBJECTIVE

Researchers have demonstrated that sleep deprivation can impair sustained attention. Most studies about sustained attention mainly focused on the effects of total sleep deprivation, since experiments on chronic sleep deprivation take more time and are more expensive. However, different effects of total sleep deprivation and chronic sleep deprivation have been observed. Specifically, studies have revealed that the chronic sleep deprivation can induce much longer time of constant impairments in certain cognitive tasks, and require more time to recover (Basner et al., 2013; Belenky et al., 2003; Van Dongen et al., 2003). Given that chronic sleep deprivation has been observed more commonly in contemporary society than total sleep deprivation (Basner et al., 2007), it is more practical to study the effects of chronic sleep deprivation. Thus, there still exists a need to investigate how chronic sleep deprivation impairs human sustained attention.

Previous studies mainly focused on the brain functional segregation through investigating neural activity changes of brain regions induced by sleep deprivation. However, given the interdependency of neural activity among brain regions, it is difficult to localize a specific function with anatomically segregated cortical areas. In addition, increasing attention has been given to study the functional integration of anatomically distributed but functionally connected brain regions (Friston, 2011; Lynall et al., 2010). Functional connectivity has been widely used to characterize brain functional integration, which measures the statistical dependencies among the neurophysiological events of the human brain (Friston, 2011). With fMRI data, functional connectivity is usually obtained as the correlation coefficients between BOLD signals of brain regions acquired during cognitive tasks or in the resting state (Park & Friston, 2013). Further, there is increasing evidence that functional connectivity is non-stationary, suggesting the dynamic property of brain functional networks. Such a dynamic property of brain networks may reveal more information about the human brain. To the best of our knowledge, no previous study has investigated the effects of chronic sleep deprivation from the perspective of brain dynamic functional connectivity.

Given dynamic functional connectivity, the human brain can be modeled as a series of functional networks. Graph theoretic analysis has been widely applied to investigate the properties of brain functional networks, with network measures of clustering coefficient and characteristic path length. However, no study has compared those network measures of brain dynamic functional networks between the rested wakefulness condition and the chronic sleep deprivation condition. Moreover, no published study has investigated the dynamic topology of brain functional networks during sustained attention in the sleep deprivation condition. The dynamic property of network measures (i.e., clustering coefficient and characteristic path length) and network topology need further investigation.

Therefore, the objective of this thesis is to investigate the effects of chronic sleep deprivation on sustained attention from the perspective of brain dynamic functional connectivity.

CHAPTER 4: RESEARCH EXPERIMENT AND DATA

The experiment was conducted by Department of Cognitive Neuroscience and Neuroergonomics at Jagiellonian University, Krakow, Poland (Fafrowicz, 2012).

4.1 Participants

Thirteen healthy female participants (mean age 23.4±2.0 years) completed this study. All of them met the experimental requirements, including right-handed, right-eye dominant, normal or corrected-to-normal visual acuity, no physical or psychiatric disorders, and no sleep related disorders. Two participants were excluded due to equipment problems. The average self-reported sleep duration was longer than 6.5 hours per night for the month before the experiment. All participants were provided with written consent and paid for their participation. This study was approved by the Bioethics Committee at Jagiellonian University.

4.2 Experiment Protocol

Participants completed the study with three visits: 1) a practice session, 2) after a week with unrestricted, fully restorative sleep - rested wakefulness session (RW), and 3) after a week of sleep curtailment by 30% - sleep deprivation session (SD). The order of experimental sessions (i.e., rested wakefulness session and chronic sleep deprivation session) was counterbalanced across all participants. The sessions were separated by at least two weeks to minimize the residual effects of sleep curtailment on cognitive performance when chronic sleep deprivation session proceeded the rested wakefulness session (Van Dongen et al., 2003). The participants spent experimental days in a controlled laboratory environment. A semi-constant routine protocol was applied: room temperature and light intensity were kept constant. The caloric intake and the level of motor activity of all subjects were controlled. Caffeine intake was banned; alcohol consumption during the preceding week was restricted.

4.3 Tasks

A modified spatial cueing task (Posner, 1980) was used to evaluate participants' sustained attention in both the rested wakefulness condition and the chronic sleep deprivation conditions. Participants were instructed to direct their attention and gaze from fixation point to targets during three types of tasks. Figure 2 illustrates the procedure of a congruent task, in which a cue (the first red dot) appeared on the same side of target (the second red dot). In contrast, an incongruent task had a cue presenting on the opposite side of target, as shown in Figure 3. During these two tasks, the subjects were required to only gaze at the targets. In addition, there would be no cue presented during the third task.

The task comprised of trials with cues congruent to a target (58%), the trials with cues incongruent to a target (15%), and trials without a cue (27%). The trial sequence was pseudo-randomized to counterbalance the presentation of each trial type. Targets were presented for 500 ms, whereas cues were presented for 300 ms. Average inter-stimulus interval was 550 ms (varying between 300-800 ms in steps of 100 ms), while the average inter-trial interval was 2800 ms (varying between 1300 and 4300 ms in steps of 500 ms). To improve sampling rate of the hemodynamic response, the phase of the target was varied relative to the image acquisition (Josephs et al., 1997; Toni et al., 1999) resulting in the final temporal resolution of 100 ms. Participants performed their tasks during four magnetic resonance scanning sessions conducted in one day. Each session comprised of 598 trials and lasted about 40min.

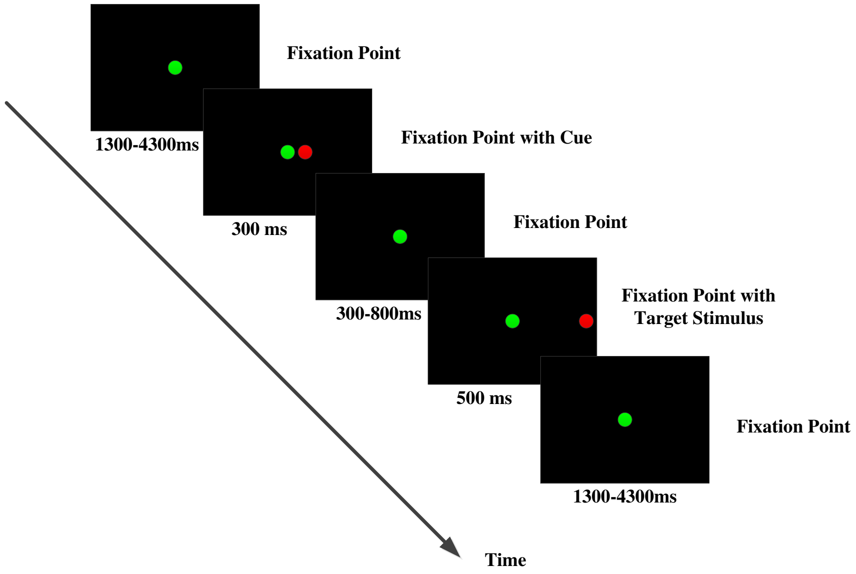


Figure 2. Illustration of Congruent Task

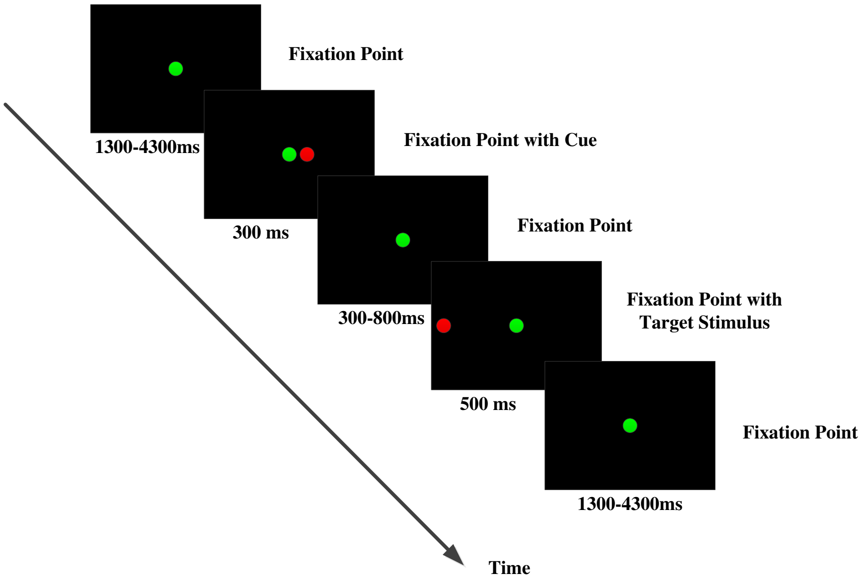


Figure 3. Illustration of Incongruent Task

4.4 Eye-tracking data collection and preprocessing

The position of an eye was monitored using a Saccadometer Research MRI system (Ober-Consulting, Poland). The system registered right eye movements using direct near-infrared technology. It used 500 Hz sampling frequency, measuring range ±20 degrees of visual angle and average spatial resolution of 15 degrees. Stimuli generated by red laser diodes were presented in the horizontal axis on a panel integrated with the saccadometer system attached to the subject's head approximately 3cm from the subject's eyes, as shown in Figure 4. There were five diodes on the panel: central diode for fixation, left and right diodes at 5 degrees and 15 degrees of visual angle for cue stimuli and target respectively. A calibration procedure before each session was conducted - the participants looked three times at each stimulus for a 1s period.

Eye-tracking data were analyzed using Research Analyzer software (Ober-Consulting, Poland). Saccades were detected with the velocity criteria: the beginning of a saccade was marked when an eye movement was faster than 5 degrees per second and this movement was classified as a saccade only when its velocity reached 90 degrees per second. SRT was defined as a difference between target appearance and the beginning of a saccade. Reaction was classified as correct when a saccade reached a target during its presentation.

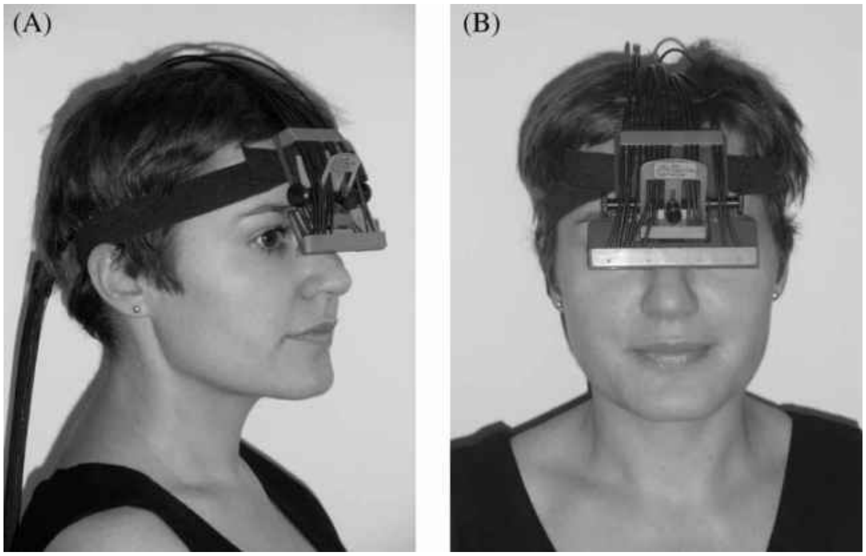


Figure 4. Eye Tracking System (Fafrowicz et al., 2010)

4.5 fMRI data collection and preprocessing

Magnetic resonance imaging (MRI) was performed using a 1.5 T Signa HDxt MRI scanner (GE Medical Systems, Milwaukee, USA). High-resolution whole-brain anatomical images were acquired using T_1-weighted multi-echo volumetric MRI and a total of 60 axial slices were obtained (matrix size $= 512 \times 512$; time repetition TR = 25.0 s; time echo TE = 6.0 ms; field of view FOV = 22×22 cm^2; flip angle $= 45^\circ$). BOLD functional scans were acquired with a T_2^*-weighted EPI pules sequence (matrix size $= 128 \times 128$; TR = 3.0 s; TE = 60ms; flip angle $= 90^\circ$). Whole brain image was covered with 20 axial slices, taken at an interleaved fashion.

All fMRI data were preprocessed using AFNI software. The first three volumes in each run were excluded because of the T_1-equilibration effects. Data were corrected for order of slice-dependent acquisition. The head motion was corrected within and across scans by reregistration.

CHAPTER 5: METHODOLOGY

This section describes the methodology and procedure used in this thesis. First, an automated anatomical labelling atlas was used to segment the human brain into different regions. The activation of an individual region was estimated as the average of voxels' activations within the given region. Then, sliding-window correlation coefficients were calculated to assess the relation between brain regions. Further, a partial least squares approach with sliding-window correlations was used, to determine significant functional connectivity related to the rested wakefulness condition and the chronic sleep deprivation condition. The functional connectivity was estimated as weighted correlation coefficients.

With the estimated functional connectivity between brain regions by sliding-window, the brain was modeled as a series of dynamic functional networks in each experimental condition. Next, a graph theoretic analysis was performed to study and compare the properties of brain functional networks between the rested wakefulness condition and the chronic sleep deprivation condition. The network measures included clustering coefficient and characteristic path length, which have been widely used to measure network functional segregation and integration, respectively. Moreover, the topology of brain dynamic functional networks was assessed with small-world topology index in the rested wakefulness condition and the chronic sleep deprivation condition.

5.1 Automated Anatomical Labeling

The fMRI data of individual subjects was corregistrated with corresponding anatomical data in the preprocessing procedure. This corregstrated functional data of the brain was then segmented into distinct regions with the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). The objective of this procedure was to simplify the fMRI data from voxel level to regional level.

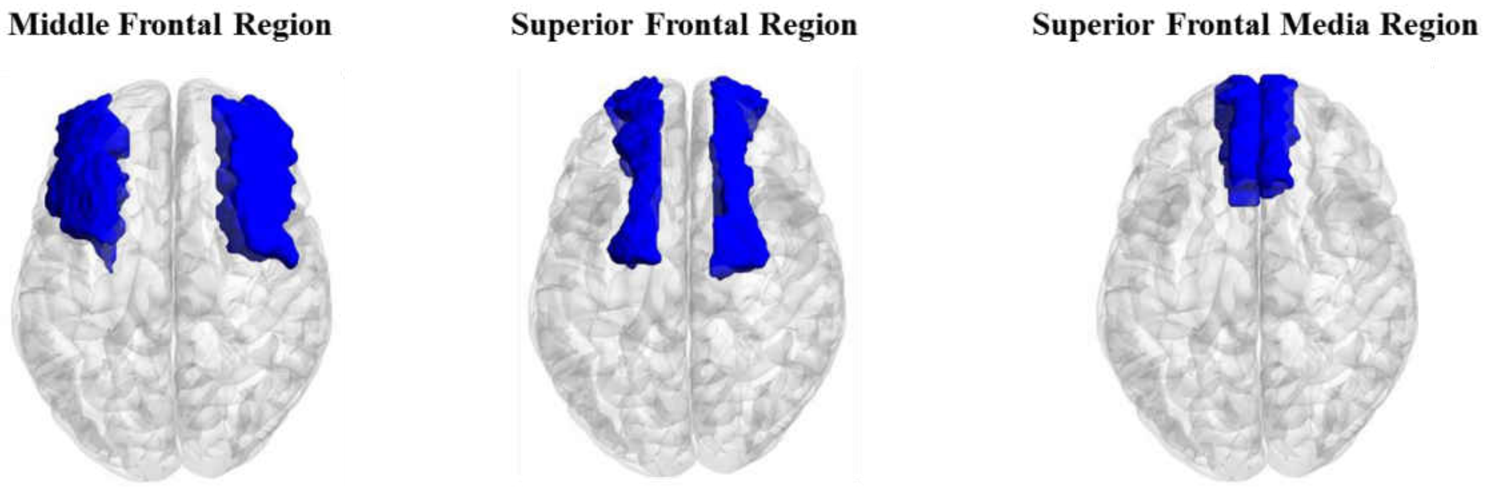
This segmentation procedure was conducted with a Matlab library developed by Singh et al. (2005). AAL is a macroscopical anatomical parcellation method that divided human brain into 90 anatomical regions of interest (Tzourio-Mazoyer et al., 2002).The three-dimension coordinates of single imaging voxel is used to determine which brain region this voxel belonged to.

In this thesis, 20 labelled regions of interest were used because of imaging quality. The brain regions are listed in Table 1. The last column shows the order of brain regions used in the following analysis. The coordinates of each brain region represent the location in the human brain, according to the brain network visualization toolbox (Xia et al., 2013).

Table 1. List of AAL Brain Regions

Lobe	AAL Brain Regions	Coordinates (mm)			Region No.
		x	y	z	
Frontal Lobe	Middle Frontal Left	-30.65	50.43	-9.62	1
	Middle Frontal Right	33.18	52.59	-9.62	2
	Superior Frontal Left	-16.56	47.32	-13.31	3
	Superior Frontal Medial Left	-7.63	-25.36	70.07	4
	Superior Frontal Medial Right	7.48	-31.59	68.09	5
	Superior Frontal Right	18.49	48.10	-14.02	6
Parietal Lobe	Inferior Parietal Left	-42.80	-45.82	46.74	7
	Inferior Parietal Right	46.46	-46.29	49.54	8
	Superior Parietal Left	-23.45	-59.56	58.96	9
	Superior Parietal Right	26.11	-59.18	62.06	10
	Precuneus Left	-7.24	-56.07	48.01	11
	Precuneus Right	9.98	-56.05	43.77	12
	SupraMarginal Left	-55.79	-33.64	30.45	13
Occipital Lobe	Middle Occipital Left	-32.39	-80.73	16.11	14
	Superior Occipital Left	-16.54	-84.26	28.17	15
	Cuneus Left	-5.93	-80.13	27.22	16
Central Region	Postcentral Left	-38.65	-5.68	50.94	17
	Postcentral Right	41.37	-8.21	52.09	18
	Precentral Left	-42.46	-22.63	48.92	19
	Precentral Right	41.43	-25.49	52.55	20

The following figures illustrate the listed brain regions in the human brain. Different colors represent different brain lobes.

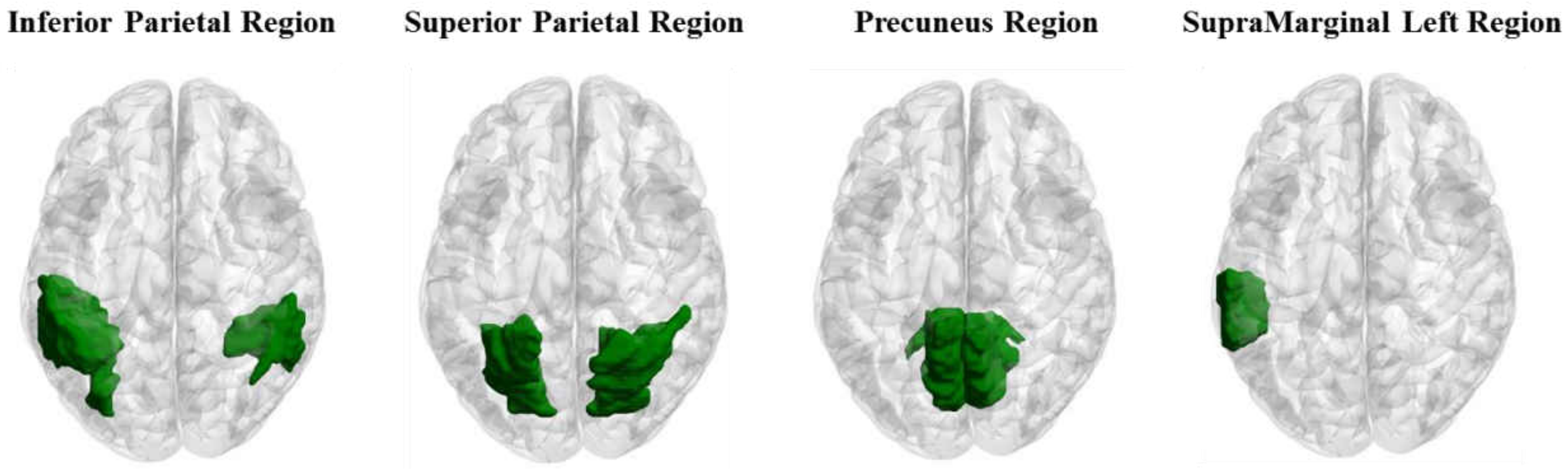


Middle Frontal Region

Superior Frontal Region

Superior Frontal Media Region

Figure 5. Illustration of Listed Brain Regions in the Frontal Lobe



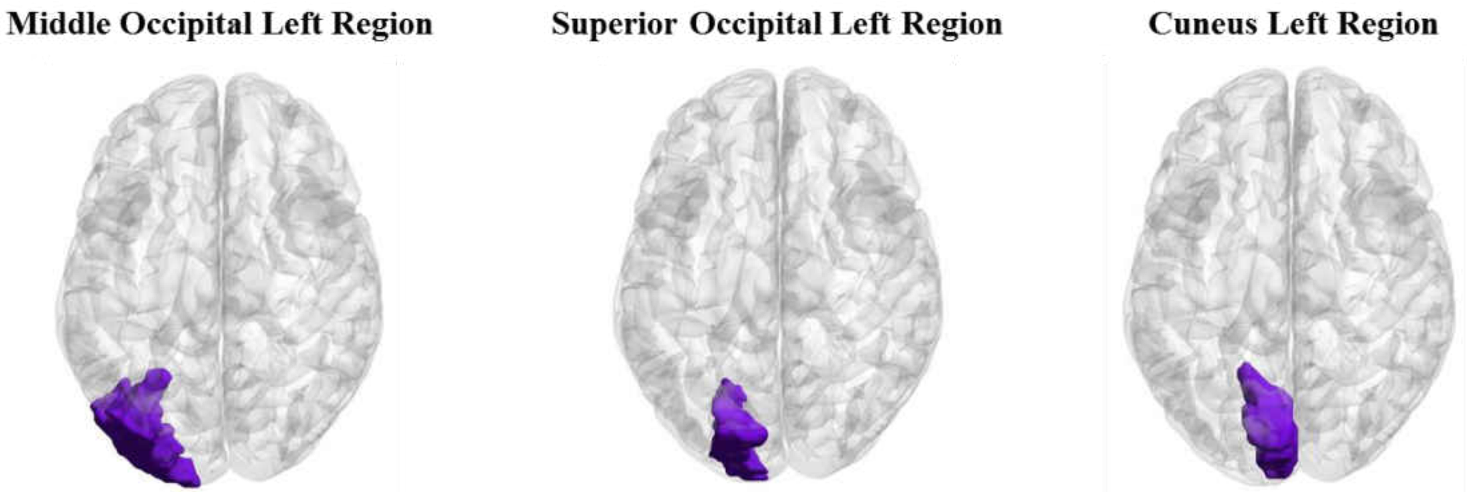
Inferior Parietal Region

Superior Parietal Region

Precuneus Region

SupraMarginal Left Region

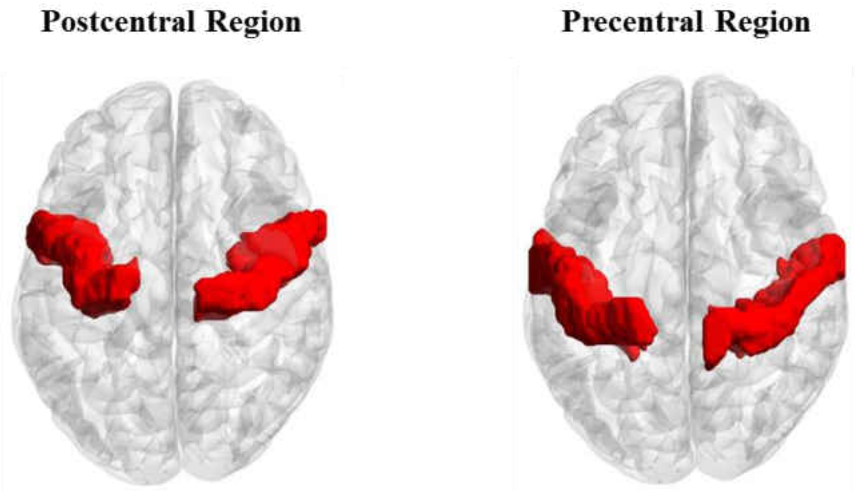
Figure 6. Illustration of Listed Brain Regions in the Parietal Lobe


Middle Occipital Left Region

Superior Occipital Left Region

Cuneus Left Region

Figure 7. Illustration of Listed Brain Regions in the Occipital Lobe


Postcentral Region

Precentral Region

Figure 8. Illustration of Listed Brain Regions in the Central Region

After segmenting, each region was composed of several imaging voxels. The activation of individual brain regions was estimated by averaging the BOLD signals across voxels within the given region. For instance, Figure 9 illustrates the procedure to estimate the activation of the left Inferior Parietal Region (the blue area). First, voxels within this region are selected through comparing their coordinates to AAL atlas. The yellow dots represent three examples of imaging voxels within this region. Then, the average of voxels' time series BOLD signals is used to represent the activation of the left Inferior Parietal Region over time.

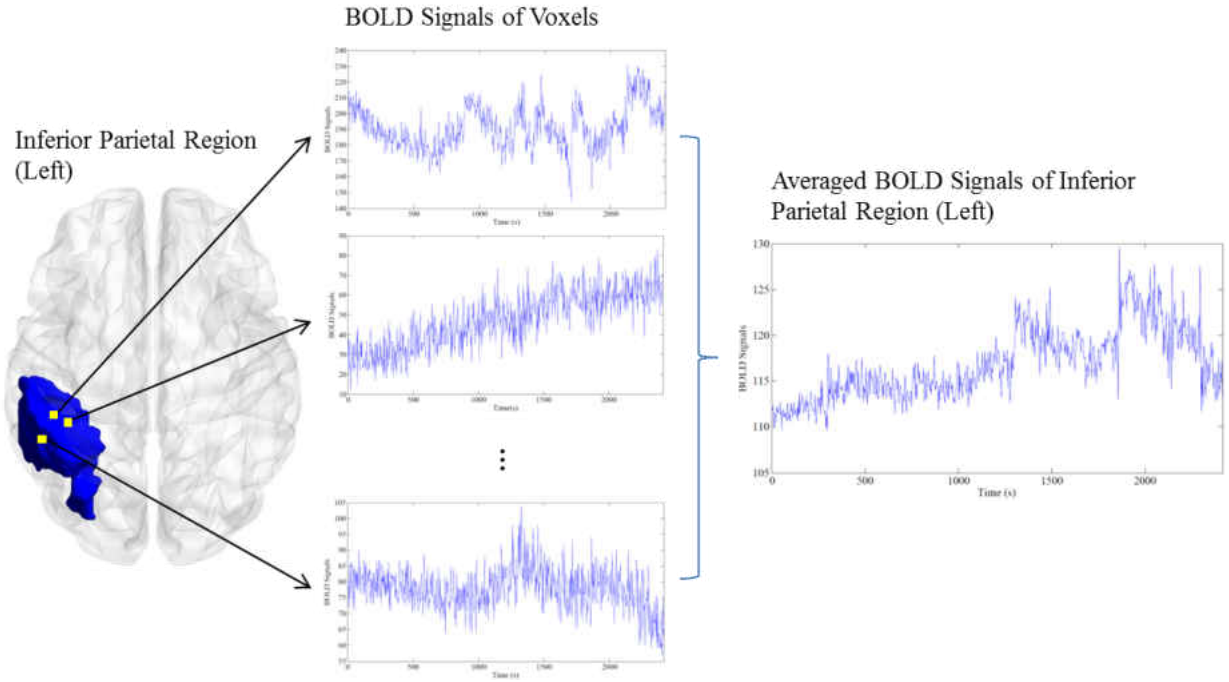


Figure 9. An Example of Estimating Regional Activation after AAL Segmentation

5.2 Sliding-Window Pearson Correlation Coefficient

The relationship between brain regions was measured as the Pearson correlation coefficient between regional BOLD signals. The correlation coefficient was calculated as follows:

$$\rho_{xy} = \frac{cov(x,y)}{\sigma_x \sigma_y} \tag{5.1}$$

where x and y denoted series BOLD signals of two brain regions. This calculation required more than one point for both x and y. In other words, the correlation coefficient represented the correlation between two brain regions during a given time interval. In this thesis, the correlation yielded a 20×20 matrix for each interval. For instance, for a given time interval, the correlation coefficient between Inferior Parietal Region (left) and Superior Frontal Region (left) is calculated and stored in the correlation matrix, as illustrated in Figure 10.

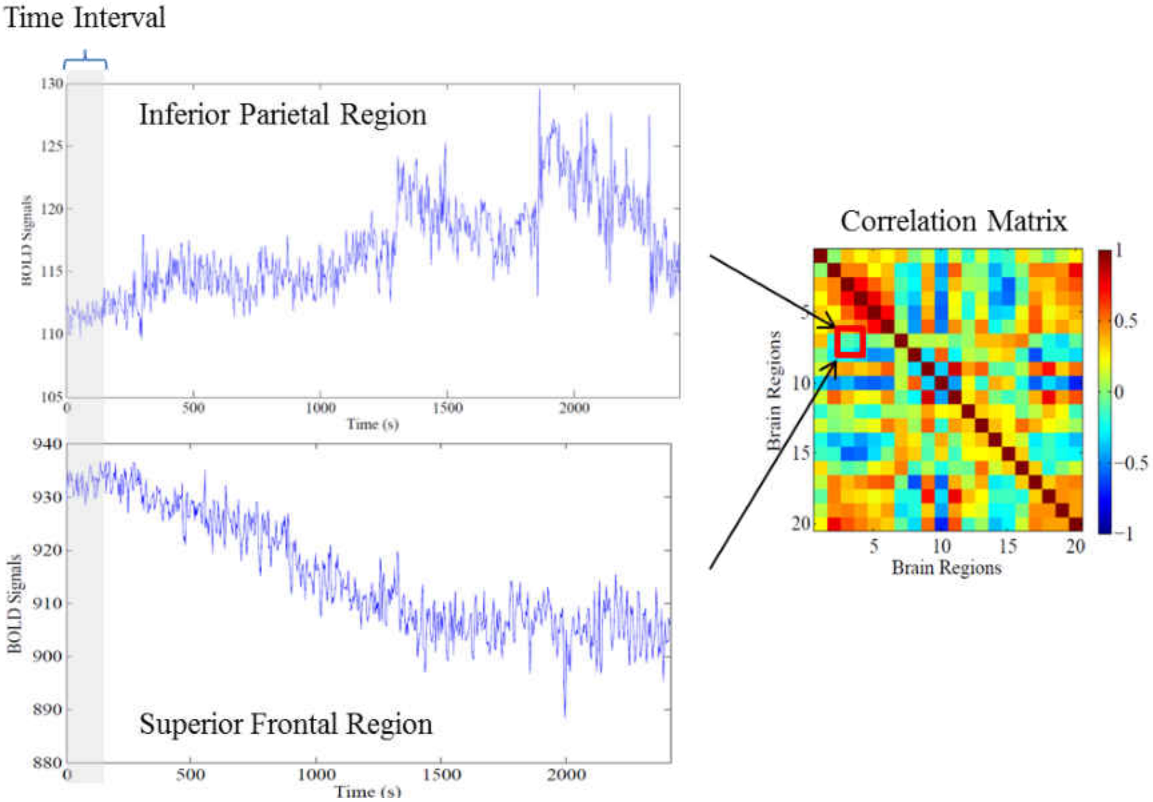


Figure 10. An Example of Calculating Pearson Correlation Coefficient

To investigate the dynamic property of the human brain, a sliding-window approach was combined with Pearson correlation coefficient. The sliding-window approach has been used in the past to study dynamic functional connectivity of the human brain (Allen et al., 2014; Bassett et al., 2011; Chang & Glover, 2010; Handwerker et al., 2012; Hutchison et al., 2013b). In this approach, each window has a fixed length of time interval; and data within this window are used to calculate the correlation coefficients. Then the window is shifted in temporal dimension by a fixed length of time, whose length determines the overlap between successive windows.

The correlation coefficient between two sliding-window series x and y is computed as follows:

$$\rho_{xy}(w) = corr(x[w_t, w_t + \Delta w], y[w_t, w_t + \Delta w]) \tag{5.2}$$

where w_t represents the first scan of a given window and Δw the length of shifted windows (Leonardi et al., 2013). According to the previous studies, cognitive states may be correctly estimated based on covariance matrices with window sizes around 30-60 scans (Hutchison et al., 2013a; Shirer et al., 2012). In this thesis, sliding-window correlation coefficients were calculated with lengths of window equal to 30 scans (each scan took 3 seconds) and shifted by two scans for each step (Figure 11). With a total of 805 scans, 388 sliding-windows were used to further investigate the property of the human brain over time.

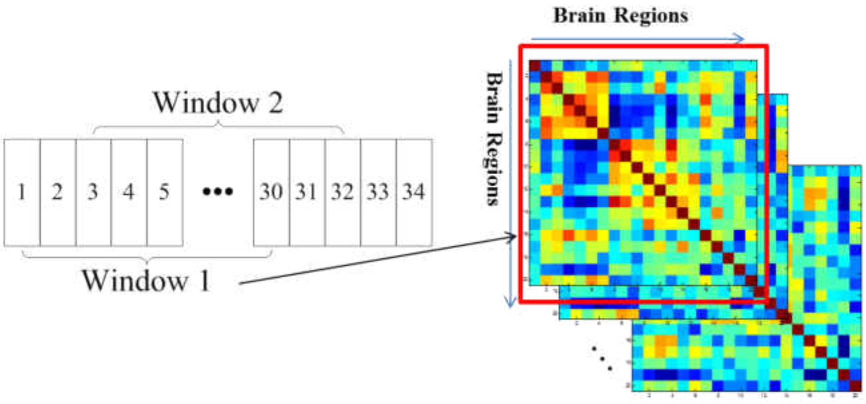


Figure 11. Sliding-Window Pearson Correlation Coefficient

5.3 Partial Least Squares Approach

A partial least squares approach was used to identify functional connectivity in the rested wakefulness condition and the chronic sleep deprivation condition.

Partial least squares (PLS) approach is a multivariate analysis that aims to investigated shared information, through determining the maximum covariance between two types of datasets (Tucker, 1958). The first application of partial least squares to neuroimaging data was conducted by McIntosh et al. (1996). This approach was then extended to spatio-temporal partial least squares with fMRI data in 2004 (McIntosh et al., 2004). This extension enables the inferences about relationships between brain activity and human behavioral performance or experimental designs across spatial and temporal dimensions (Lin et al., 2003).

In the previous application of partial least squares to fMRI data, the objective was to determine brain activation patterns related to experimental designs or behavioral measures. A journal paper, which applied principal component analysis (PCA) to functional connectivity (Leonardi et al., 2013), provided the motivation for extending the application of PLS to identifying patterns of functional connectivity.

5.3.1 Notation

Matrices are represented by upper case bold letters (e.g., $\mathbf{X}$), whereas column vectors are represented by lower case bold letters (e.g., $\boldsymbol{x}$). The transpositions of matrices or column vectors are represented by an uppercase superscript T (e.g., $\mathbf{X}^{\mathrm{T}}$). The uppercase italic letters (e.g., I) represent the total number of rows, columns, or subjects; and a given row, column, or subject is represented by a lower case italic letter (e.g., i).

5.3.2 Data Organization

In partial least squares approach, input data were stored in two matrices, brain connectivity matrix (**X**) and design matrix (**Y**). In both matrices, a row represented an observation of one subject in one of the experimental conditions. In this thesis, we had two experimental conditions (*K*=2) and 11 subjects (*I*=11). Thus, the degree of freedom in the experimental design was $K - 1 = 1$.The design matrix (**Y**) was constructed as a 22×1 design contrast matrix as follows:

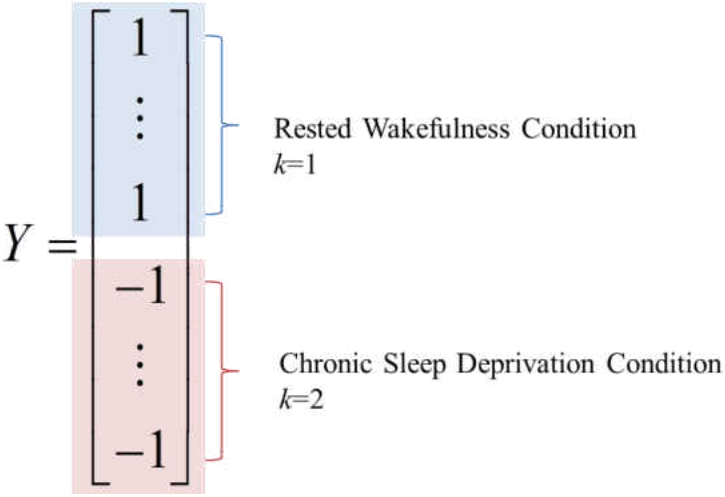


Figure 12. Design Matrix (**Y**) of Partial Least Squares Approach

Individual connectivity matrices ($\mathbf{C}_{i,k}$) were created to construct the brain connectivity matrix. As demonstrated in Figure 13, a correlation matrix of sliding-window w_t is vectorized into a column vector $\mathbf{c}_{i,t,k}$, where *i* denotes the subject, *t* the sliding window, and *k* the experimental condition. For instance, $\mathbf{c}_{1,10,1}$ represents the first subject's connectivity vector of the tenth sliding-window in the rested wakefulness condition.

When transforming the correlation matrix, only the upper triangular part was kept due to matrix symmetry, resulting in $(N^2 - N)/2$ pairs of connectivity, where N represented the number of brain regions ($N = 20$). As a result, an individual connectivity matrix had dimensions of 190×388 in each condition, where 388 was the total number of sliding-windows.

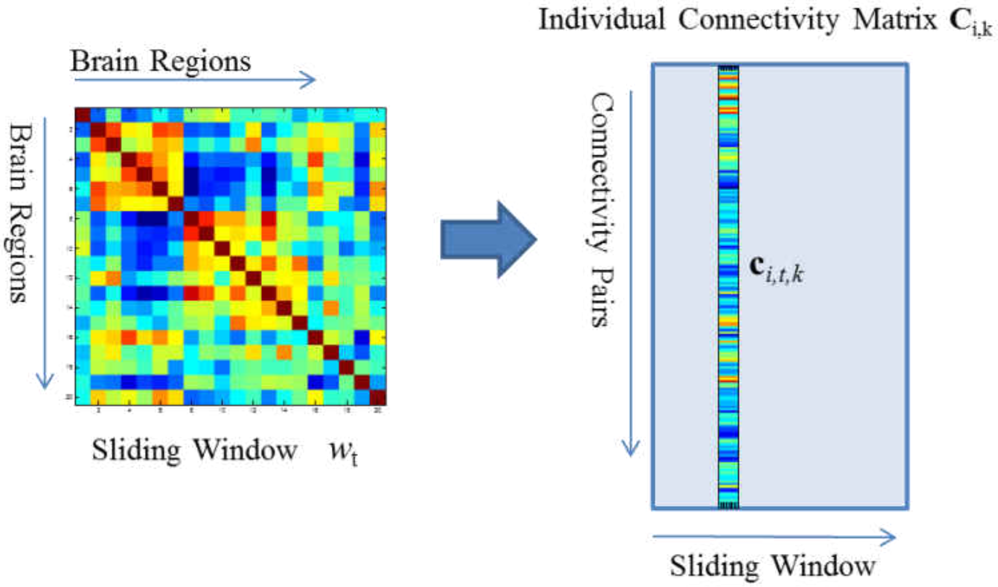


Figure 13. Illustration of Constructing Individual Connectivity Matrix with Sliding-Window Correlation Matrix

The vectors of individual connectivity matrices were then extracted and reorganized within sliding-window blocks. As illustrated in Figure 14, connectivity vectors of subject 2 ($\mathbf{c}_{2,2,1}$) and subject 5 ($\mathbf{c}_{5,2,1}$) in the second sliding-window are transformed and reorganized into row vectors of the second window block in the rested wakefulness condition.

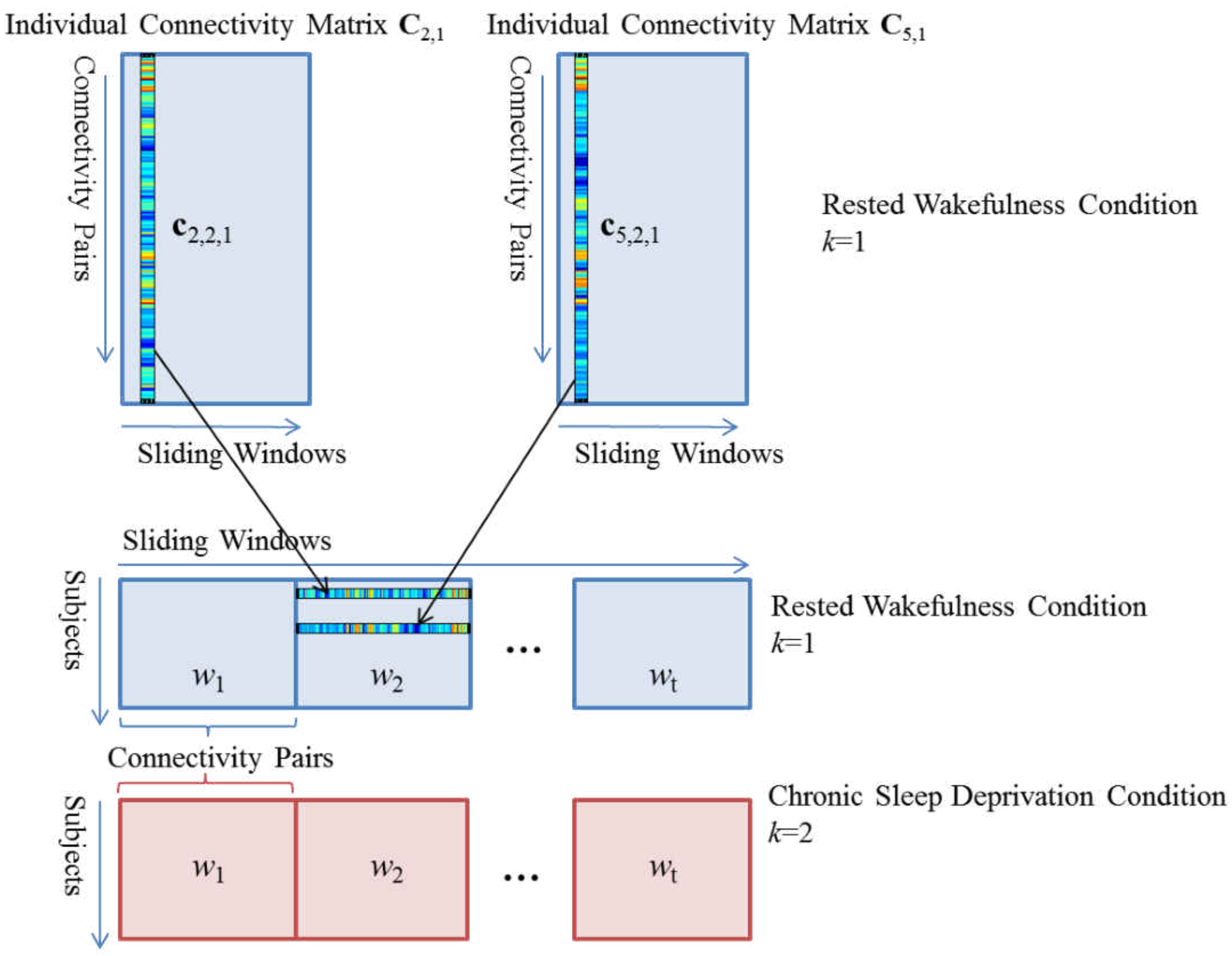


Figure 14. Illustration of Constructing Brain Connectivity Matrix (**X**) with Individual Connectivity Matrices

In this way, the brain connectivity matrix was composed of a series of window blocks, which contained correlation coefficients between pairs of brain regions. These blocks were ordered by experimental conditions. In Figure 15, where $\mathbf{X}_t$ denotes a connectivity submatrix of sliding-window t, the brain connectivity matrix ($\mathbf{X}$) can be represented as a composition of these submatrices as $\mathbf{X} = [\mathbf{X}_1, \mathbf{X}_2, \cdots, \mathbf{X}_{388}]$.

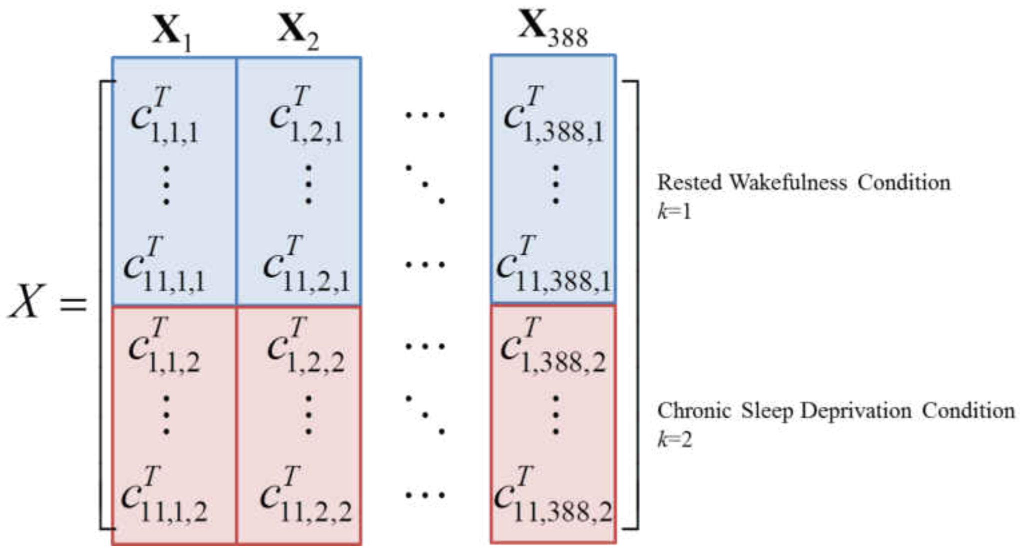


Figure 15. Data Organization of Brain Connectivity Matrix (**X**)

To simplify computation, the submatrix of the brain connectivity matrix ($\mathbf{X}_t$) was used individually as input in the following analysis. Partial least squares approach can relate the submatrix to the design matrix for each sliding-window. Every step of singular value decomposition was repeated for all the sliding-windows, where $T = 388$.

5.3.3 Singular Value Decomposition

The brain connectivity submatrix ($\mathbf{X}_\mathrm{t}$) and design matrix ($\mathbf{Y}$) were statistically centered and normalized in order to make the variables comparable. The normalized matrices were denoted as $\mathbf{RX}_t$ for brain connectivity and $\mathbf{RY}$ for experimental design. Then a cross-product matrix was calculated to relate the brain connectivity submatrix ($\mathbf{RX}_t$) with the design matrix ($\mathbf{RY}$), denoted as $\mathbf{R}_t$:

$$\mathbf{R}_t = (\mathbf{RY})^T(\mathbf{RX}_t) \tag{5.3}$$

The goal of partial least squares was to find a set of orthogonal latent variables with maximal covariance between two input data. Singular value decomposition (SVD) was used as a tool to identify those latent variables. This method decomposed matrix $\mathbf{R}_t$ into three matrices:

$$\mathbf{R}_t = \mathbf{U}_t\Delta_t\mathbf{V}_t^\mathrm{T} \tag{5.4}$$

The matrix Δ_t was a diagonal matrix of nonzero values. Since the degree of freedom in design contrast was one (Figure 12), matrix Δ_t contained only one nonzero singular value (δ_t). This value was eigenvalues that indicated the amount of the covariance between connectivity and the experimental design by each latent variable.

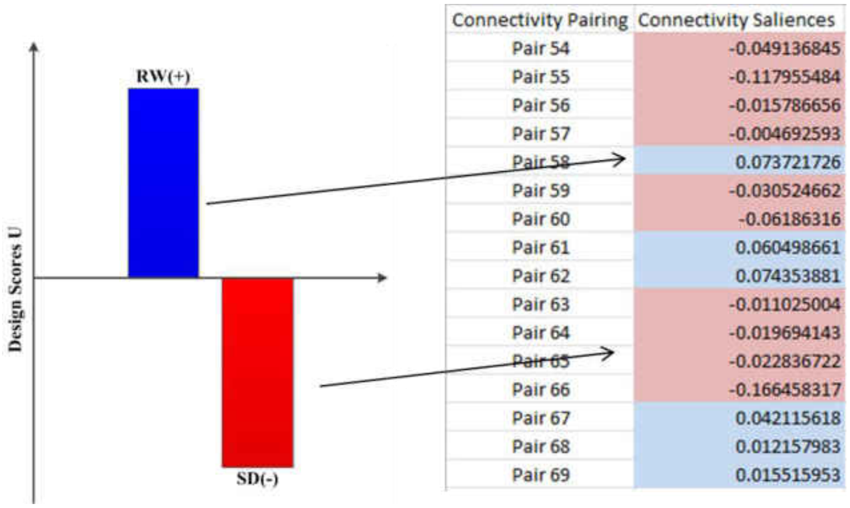
The singular matrix $\mathbf{U}_t$ was called design salience and $\mathbf{V}_t$ the connectivity salience, which represented experiment profiles and brain connectivity respectively, with the best characterization of $\mathbf{R}_t$. These two salience matrices were orthonormal matrices (i.e., $\mathbf{U}_t^\mathrm{T}\mathbf{U}_t = \mathbf{V}_t^\mathrm{T}\mathbf{V}_t = \mathbf{I}$). When projecting the original matrices $\mathbf{RX}_t$ and $\mathbf{RY}$ onto their corresponding saliences, latent variable was obtained for brain connectivity ($\mathbf{RX}_t$), called "connectivity scores", as follows:

$$\mathbf{L}_{X,t} = (\mathbf{RX}_t)(\mathbf{V}_t) \tag{5.5}$$

and for experiment design ($\mathbf{RY}$), called "design scores", as follows:

$$\mathbf{L}_{\boldsymbol{Y},t} = (\mathbf{RY})(\mathbf{U}_t) \tag{5.6}$$

Since the original design matrix ($\mathbf{Y}$) contains both positive (rested wakefulness condition) and negative (chronic sleep deprivation condition) values (see Figure 12), connectivity salience is decomposed into two groups, as illustrated in Figure 16. The connectivity with positive salience is related to the rested wakefulness condition; while the connectivity with negative salience is related to the chronic sleep deprivation condition. In this way, the connectivity was identified for each experimental condition in each sliding-window.



Connectivity Pairing	Connectivity Saliences
Pair 54	-0.049136845
Pair 55	-0.117955484
Pair 56	-0.015786656
Pair 57	-0.004692593
Pair 58	0.073721726
Pair 59	-0.030524662
Pair 60	-0.06186316
Pair 61	0.060498661
Pair 62	0.074353881
Pair 63	-0.011025004
Pair 64	-0.019694143
Pair 65	-0.022836722
Pair 66	-0.166458317
Pair 67	0.042115618
Pair 68	0.012157983
Pair 69	0.015515953

Figure 16. Example of Relating Connectivity to Experimental Condition through Design Scores

The statistical significance of the decomposition was assessed using a permutation test. In this test, rows of connectivity submatrix ($\mathbf{RX}_t$) were resampled without replacement to reassign experimental condition to subjects. In this thesis, 500 times permutation test was used for each sliding-window t, and the permutated connectivity submatrix was denoted as $\mathbf{RX}_{perm,t}$. Then SVD was re-performed with the new sampled matrix, as follows:

$$\mathbf{R}_{perm,t} = (\mathbf{RY})^T\left(\mathbf{RX}_{perm,t}\right) = \mathbf{U}_{perm,t}\Delta_{perm,t}\mathbf{V}_{perm,t}^{\mathrm{T}} \tag{5.7}$$

The probability of significant decomposition was determined by the number of times that permutated eigenvalues ($\delta_{perm,t}$) exceeded the original eigenvalue (δ_t) over total times of permutation:

$$p_t = \frac{times(\delta_{perm,t} > \delta_t)}{500} \tag{5.8}$$

This probability was calculated for each sliding window, and the corresponding decomposition was considered significant when $p_t < 0.05$.

5.3.4 Brain Functional Connectivity Estimation

To estimate the functional connectivity, significant connectivity that was reliable with experimental conditions was selected. Bootstrap test was performed to determine the reliability of connectivity saliences through resampling rows of the connectivity submatrix ($\mathbf{RX}_t$) with replacement. A bootstrap test was used 100 times for each sliding-window t, and the bootstrapped connectivity submatrix was denoted as $\mathbf{RX}_{boot,t}$. Then singular value decomposition was re-performed with new sampled matrix, as follows:

$$\mathbf{R}_{boot,t} = (\mathbf{RY})^T(\mathbf{RX}_{boot,t}) = \mathbf{U}_{boot,t}\Delta_{boot,t}\mathbf{V}_{boot,t}^{\mathrm{T}} \tag{5.9}$$

Bootstrap ratio (BSR) of connectivity pairing j was defined as the ratio between the original connectivity salience and the standard error of bootstrapped saliences:

$$BSR_{j,t} = \frac{v_{j,t}}{SE(\Delta_{boot,t})} \tag{5.10}$$

In this way, BSRs would follow a distribution similar to T-distribution. Thus, significant connectivity was selected with the absolute value of bootstrap ratio larger than 2 (corresponding to $p < 0.05$). This connectivity was considered to be significantly reliable with experimental conditions.

In this thesis, functional connectivity $f_{j,t}$ was estimated as a weighted correlation coefficient $x_{j,t}$ (after Fisher-transformation), whose weight was equal to the corresponding connectivity salience $v_{j,t}$:

$$f_{j,t} = v_{j,t} \cdot x_{j,t} \tag{5.11}$$

where j represented the pair of connectivity, and t the sliding-window. If the connectivity was not significant in the bootstrap test, the weight of this connectivity was assigned to zero.

5.4 Construction of Brain Dynamic Functional Networks

With the application of partial least squares to brain connectivity, brain functional connectivity was estimated as a linear combination of connectivity salience and normalized correlation coefficients. In this way, the brain can be modeled as a complex network with weighted and undirected connections. The weights were equal to the estimated functional connectivity, and nodes represented brain regions.

In addition, the sliding-window approach identified a series of functional connectivity patterns across sliding-windows in each experimental condition. The brain was modeled as a series of dynamic functional networks in the rested wakefulness condition and the chronic sleep deprivation condition.

5.5 Graph Theoretic Analysis

In this section, a graph theoretic analysis was used to investigate the network properties of dynamic brain functional networks. All the network measures were based on weighted and undirected brain functional networks. In this thesis, a Brain Connectivity Toolbox with Matlab was used to implement the analyses described below (Sporns et al., 2004).

5.5.1 Clustering Coefficient

Clustering coefficient is a widely used network measure of functional segregation. It measures the prevalence of clusters in the network. To calculate this measure, first the definition of triangle has to be introduced. In graph theory, a triangle consists of three nodes that are connected by either two (open triangle) or three (closed triangle) undirected edges. In general, the number of triangles of node i in a weighted and undirected network is calculated as:

$$t_i = \frac{1}{2}\sum_{j,h\in N}\left(w_{ij}w_{jh}w_{jh}\right)^{1/3} \tag{5.12}$$

where N represents the total number of nodes, and w_{ij} the weight of connection between node i and j (Rubinov & Sporns, 2010).

The local clustering coefficient of node i is measured as the fraction of triangles around this node:

$$C_i = \frac{2t_i}{k_i(k_i-1)} \tag{5.13}$$

where k_i represents the degree of node i, which is calculated as:

$$k_i = \sum_{j\in N} w_{ij} \tag{5.14}$$

To measure the functional segregation of the entire network, the average clustering coefficient of network $\bar{C}$ is calculated as:

$$\bar{C} = \frac{1}{n}\sum_{i\in N} C_i = \frac{1}{n}\sum_{i\in N}\frac{2t_i}{k_i(k_i-1)} \tag{5.15}$$

5.5.2 Characteristic Path Length

Characteristic path length is widely used to measure the functional integration of networks. It measures the ease of communication between distinct nodes in the network. To calculate the characteristic path length, a concept of path must be introduced. In graph theory, paths are sequences of distinct nodes and edges. From the perspective of brain functional connectivity, paths represent sequences of statistical associations between pairs of brain regions. The shortest path length indicates stronger statistical associations for functional integration (Rubinov & Sporns, 2010). The shortest path length between a pair of nodes is calculated as follow:

$$d_{ij} = \min(l_{i\leftrightarrow j}) \tag{5.16}$$

where $l_{i\leftrightarrow j}$ represents all potential routes between node i and node j. In this thesis, the length between a pair of connected nodes was estimated as the reciprocal of functional connectivity. The important connection with large weight was assumed to have a short communication distance. The average shortest path length of a network is defined as the characteristic path length:

$$L = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N, i\neq j} d_{ij}}{n-1} \tag{5.17}$$

5.6 <u>Small-World Topology of Brain Functional Networks</u>

Dynamic topology was used to investigate the comprehensive property of brain functional networks. Watts and Strogatz (1998) described the small-world network by measuring two network parameters, clustering coefficient ratio (γ) and characteristic path length ratio (λ).

To calculate the ratios, a similar random network has to be first created with the same distribution of degrees as the original network. For each sliding-window, a similar random network was created for brain functional networks in the rested wakefulness condition and the chronic sleep deprivation condition, respectively. To determine the network parameters, clustering coefficient (C_{net}) and characteristic path length (L_{net}) were compared with those of the corresponding random networks (C_{random} and L_{random}):

$$\gamma = \frac{C_{net}}{C_{random}} \tag{5.18}$$

$$\lambda = \frac{L_{net}}{L_{random}} \tag{5.19}$$

The small-world topology index (δ) is defined as a ratio between clustering coefficient ratio γ and characteristic path length ratio λ:

$$\delta = \frac{\gamma}{\lambda} \tag{5.20}$$

According to the property of small-world topology, networks of this structure show a higher level of clustering coefficient, while remaining around the same length of the characteristic path, compared with random network (Rubinov et al., 2009). Hence, if a network has small-world topology, the clustering coefficient ratio should be larger than one, while characteristic path length ratio should be close to one. As a result, the index ratio δ should be larger than one in a network of small-world topology.

CHAPTER 6: RESULTS

6.1 Performance Analysis

In this thesis, subjects' sustained attention was evaluated with two categories of behavioral measures: accuracy and response time (RT). Accuracy was defined as a ratio between the number of correct responses and the total number of trials. Response time was defined as the time difference between the appearance of the target and the beginning of the saccade, if subjects accomplished the task correctly. Lapses represented responses with response times longer than 500ms.

According to the results in Table 2, chronically sleep deprived subjects showed lower accuracy than those in the rested wakefulness condition (p=0.002). Specifically, the number of lapses was significantly larger than those under rested wakefulness (p=0.016). These observations indicated that chronic sleep deprivation impaired sustained attention by decreasing response accuracy.

Table 2. ANOVA Results of Sustained Attention Performance

Measure	Rested Wakefulness	Chronic Sleep Deprivation
Accuracy (%)	81.76* ± 16.06	76.37* ± 16.34
Number of Lapses	2.00* ± 3.15	3.77* ± 3.41
Average RT (ms)	161.06 ± 19.81**	165.24 ± 26.98**
10% of Fastest RT (ms)	80.05 ± 29.56	71.05 ± 35.01
10% of Slowest RT (ms)	257.20* ± 47.59	276.82* ± 55.76

*p<.05 in paired t-tests comparing means of measures in rested wakefulness and sleep deprivation
**p<.05 in chi-square tests comparing variances of measures in rested wakefulness and sleep deprivation

From the perspective of response time, the results showed that there was no significant difference of response time between the rested wakefulness condition and the chronic sleep deprivation condition (p>0.05). Furthermore, sleep deprived subjects even show slightly better but not significant performance of the top 10% in response time ($p > 0.05$). On the contrary, the result showed increased slowest response time in chronic sleep deprivation ($p = 0.004$), which suggested that chronic sleep deprivation induced significant effects on slowest responses. In addition, the results showed larger variances of response time in the chronic sleep deprivation condition than those in the rested wakefulness condition (see Table 2).

6.2 Estimated Brain Dynamic Functional Connectivity

With the proposed methodology, brain dynamic functional connectivity was assessed using the weighted correlation coefficients. The decomposition of each sliding-window was significant with permutation tests ($p < 0.05$). The bootstrap ratios were then used to select significant connectivity. Because of the characteristic of singular value decomposition, a given pair of connectivity must be either significant or not significant. If it was significant then, it must be shown in either the rested wakefulness condition or the chronic sleep deprivation condition (see Figure 17).

In Figure 18, each subject has 190 pairs of functional connectivity between 20 brain regions over time. A given value in this figure shows the strength of estimated functional connectivity, as well as the related experimental condition. Connectivity with positive values is significant in the rested wakefulness condition; while connectivity with negative values is significant in the chronic sleep deprivation condition. The absolute values of estimated functional connectivity indicate the strengths of connectivity.

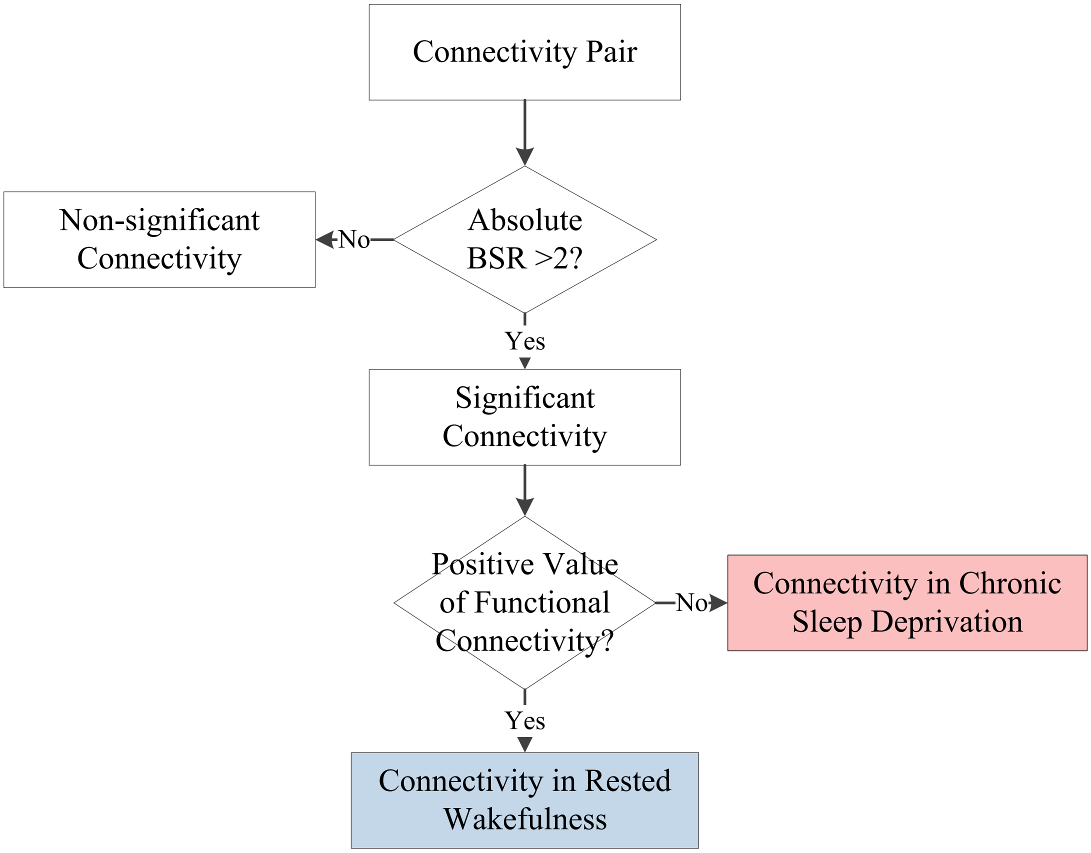


Figure 17. Illustration of Partial Least Squares Approach Outputs

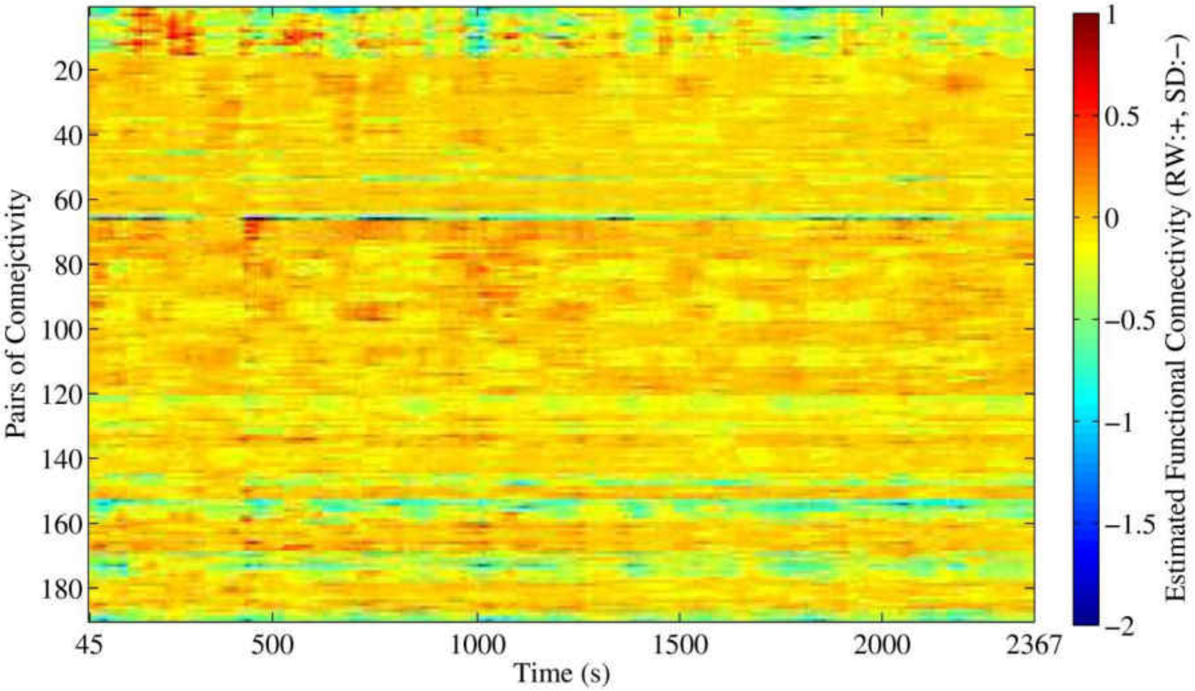


Figure 18. Estimated Dynamic Functional Connectivity

According to Figure 18, the color of each row varies over time, indicating that the strength of functional connectivity fluctuates dynamically. Especially, some functional connectivity is not stationary with the experimental condition that is changing between the rested wakefulness condition and the chronic sleep deprivation condition.

Figure 19 illustrates an example of estimated functional connectivity 39. The vertical dimension represents the absolute value of estimated functional connectivity; and the color of line indicates the related experimental condition. The strength of this connectivity is changing over time. Further, this connectivity sometimes is shown in the rested wakefulness condition, but sometimes in the chronic sleep deprivation condition. These observations illustrated the dynamic patterns of functional connectivity in both experimental conditions.

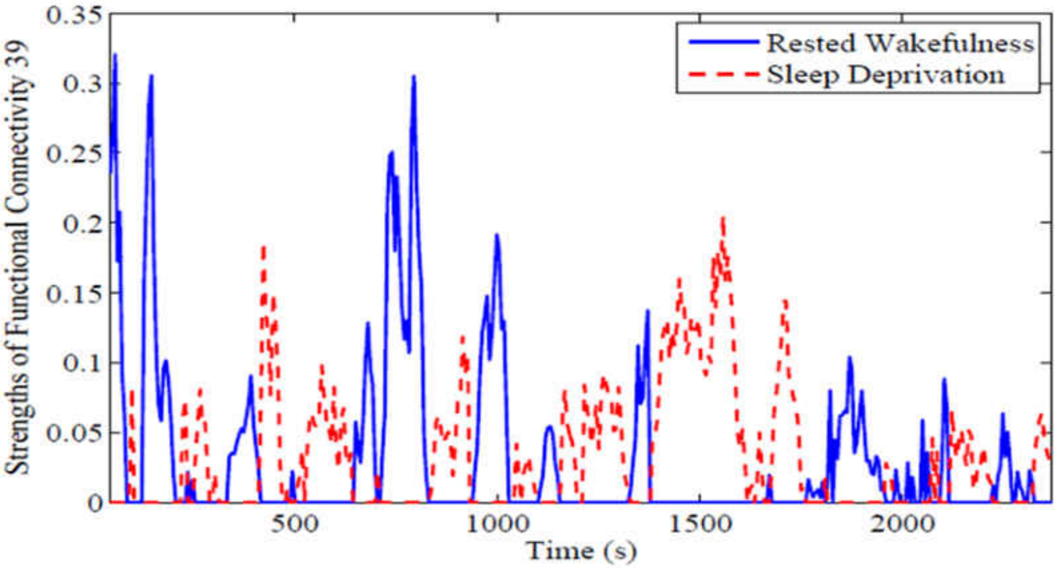


Figure 19. Example of Estimated Functional Connectivity Pair 39

A brain network visualization tool was used to visualize brain dynamic patterns of functional connectivity in brain atlas (Xia et al., 2013). Examples of three sliding-windows are illustrated in Figure 20. The left side with blue connections shows brain functional connectivity in the rested wakefulness condition; the right side with red connections shows brain functional connectivity in the chronic sleep deprivation condition. The results indicate that the brain has more connectivity in the chronic sleep deprivation condition. Further, a paired t-test showed that the number of functional connectivity in chronic sleep deprivation was significantly larger than that in rested wakefulness (p<0.001).

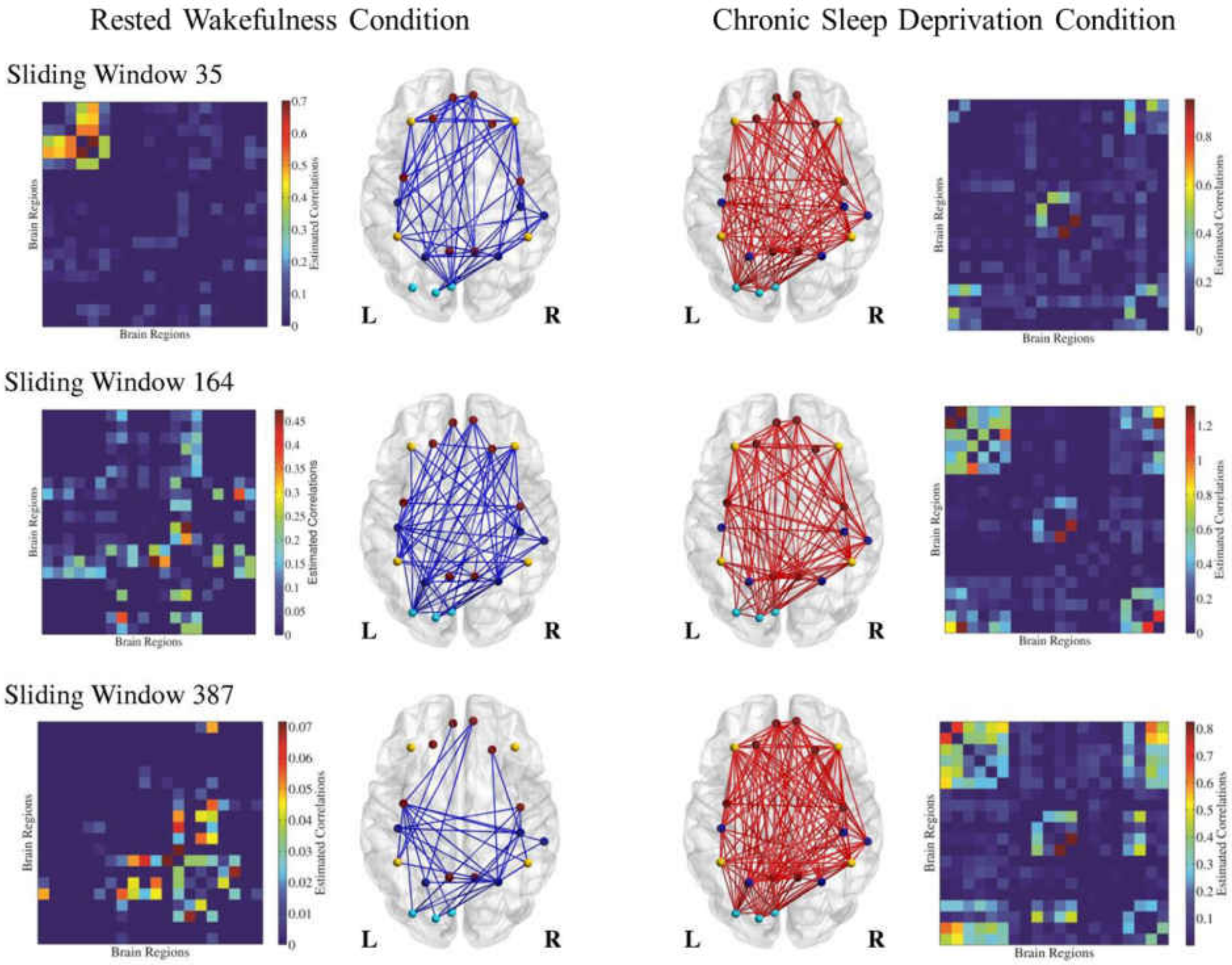


Figure 20. Three Examples of Dynamic Functional Connectivity in Brain Atlas

6.3 Graph Theoretic Analysis

With the estimated functional connectivity, brain was modeled as a series of weighted and undirected functional networks in the rested wakefulness condition and the chronic sleep deprivation condition, respectively. The nodes represented 20 brain regions as listed in Table 1, and connections represented estimated functional connectivity. In the previous section, the results showed dynamic brain functional connectivity over time. As a result, the structure of brain functional networks was changing dynamically. In this section, a graph theoretic analysis was applied to investigate the properties of brain functional networks.

6.3.1 Clustering Coefficient of Brain Functional Networks

Clustering coefficient was used as a network measure of functional segregation. The average clustering coefficients of brain functional networks were calculated and illustrated in Figure 21. The red dashed line represents the clustering coefficients in the sleep deprivation condition; while the blue line represents those in the rested wakefulness condition.

According to the results, the average clustering coefficients of brain functional networks fluctuated over time. This observation indicated that the structures of brain functional networks kept changing dynamically in both experimental conditions. Furthermore, the average clustering coefficients of brain functional networks in the chronic sleep deprivation condition were significantly higher than those in the rested wakefulness condition ($p<0.001$). On the other side, an F-test showed larger variances of clustering coefficients in the chronic sleep deprivation condition compared with those in the rested wakefulness condition ($F=1.85$, $p=0.023$).

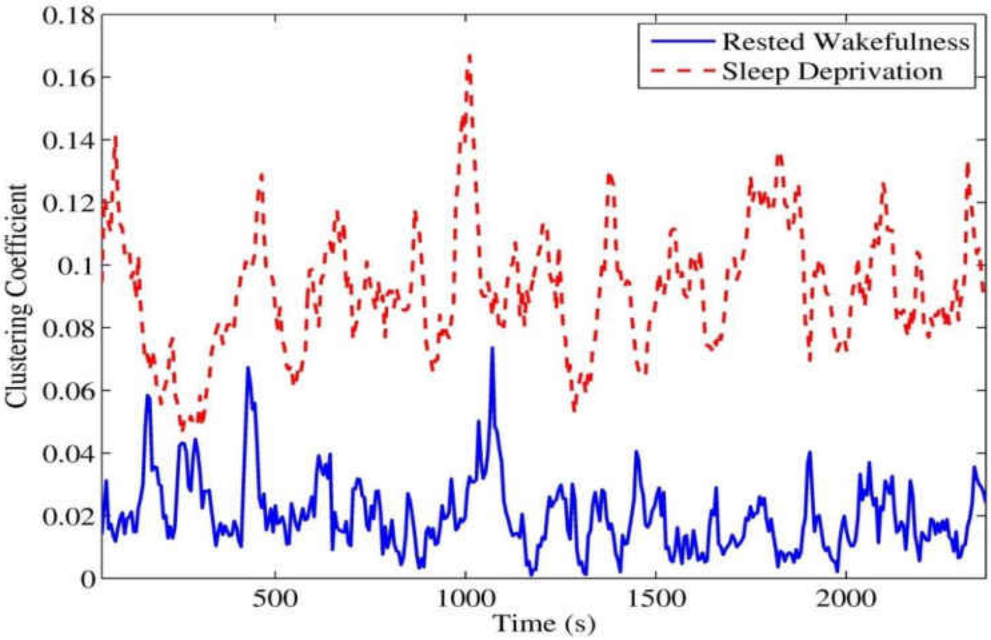


Figure 21. The Average Clustering Coefficients of Brain Functional Networks

6.3.2 Characteristic Path Lengths of Brain Functional Networks

Characteristic path length was used a network measure of functional integration. The characteristic path lengths of brain functional networks are illustrated in Figure 22. The results showed shorter characteristic path lengths of brain functional networks in chronic sleep deprivation than those in the rested wakefulness ($p<0.001$). An F-test showed that the variances of characteristic path lengths were significantly larger in the rested wakefulness condition compared with those in the chronic sleep deprivation condition ($F=2.99$, $p<0.001$).

The fluctuations of characteristic path lengths were a result of the changing structures of brain functional networks in the rested wakefulness condition and the chronic sleep deprivation condition. Thus, this result demonstrated the dynamic properties of brain functional networks, consistent with previous observations.

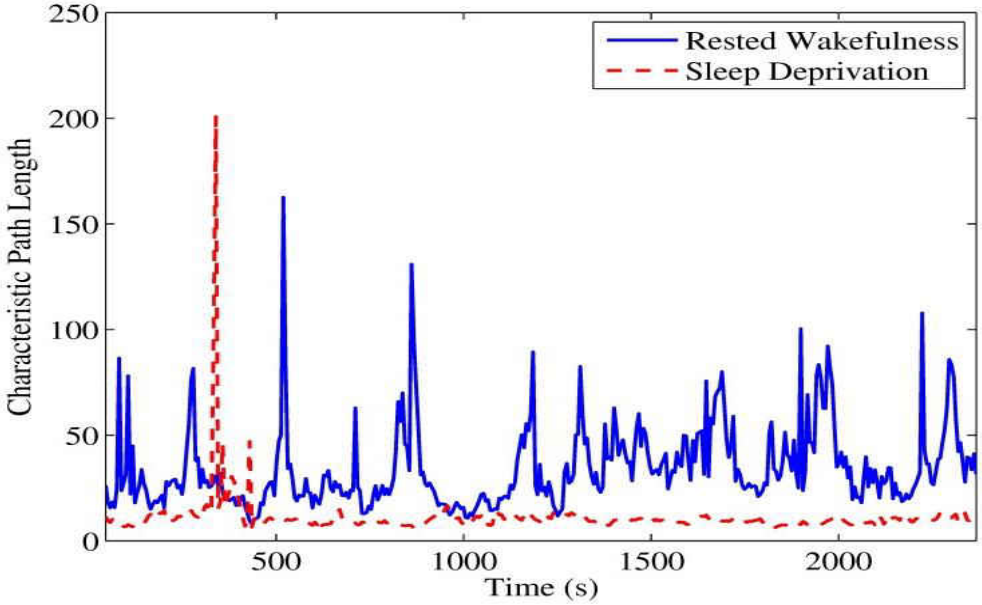


Figure 22. Characteristic Path Lengths of Brain Functional Networks

6.4 Small-World Topology of Brain Functional Networks

This section describes the topology of brain functional networks in the rested wakefulness condition and the chronic sleep deprivation condition. First, a series of similar random networks related to either the rested wakefulness condition or the chronic sleep deprivation condition were constructed. The small-world topology index (δ) was determined by two network parameters, clustering coefficient ratio (γ) and characteristic path length ratio (λ).

6.4.1 Small-World Topology Index in the rested wakefulness condition

For each sliding-window, γ was obtained as a ratio between the clustering coefficient of the brain functional network and that of the corresponding random network. The results in Figure 23 illustrate that brain functional networks ($C_{net,RW}$) have larger clustering coefficients than those of the corresponding random networks ($C_{random,RW}$) in the rested wakefulness condition

(p<0.001). As a result, the average gamma ratio (γ_{RW}) was larger than one in the rested wakefulness condition.

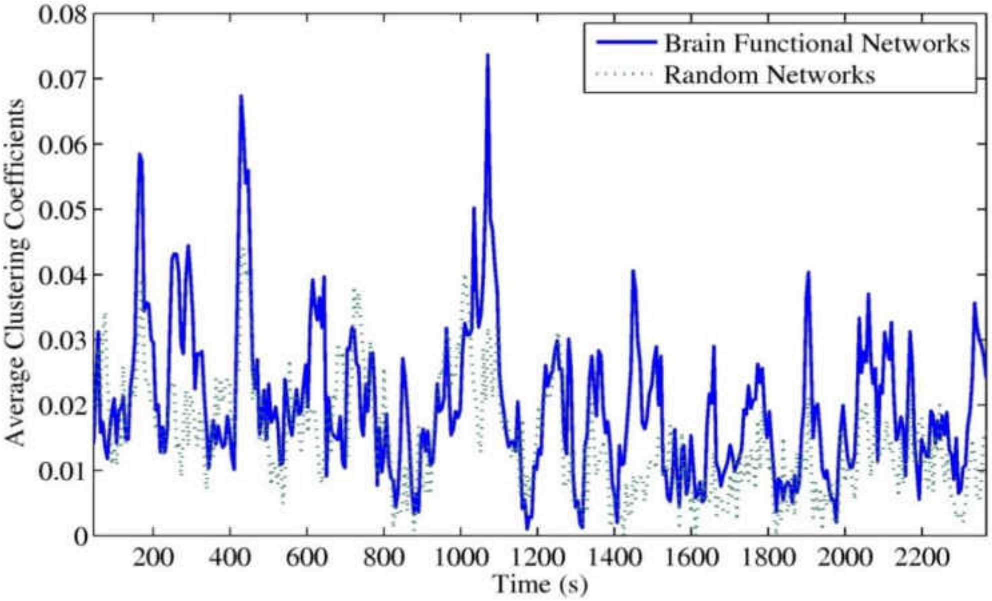


Figure 23. Clustering Coefficients of Brain Functional Networks and Similar Random Networks in the rested wakefulness condition

Lambda ratio was calculated as the characteristic path length of the brain functional network divided by that of the corresponding random network. The results are illustrated in Figure 24. The characteristic path lengths of brain functional networks ($L_{net,RW}$) were not significantly different from those of random networks ($L_{random,RW}$) in the rested wakefulness condition (p=0.99). The average ratio of characteristic path lengths (λ_{RW}) was around one in the rested wakefulness condition.

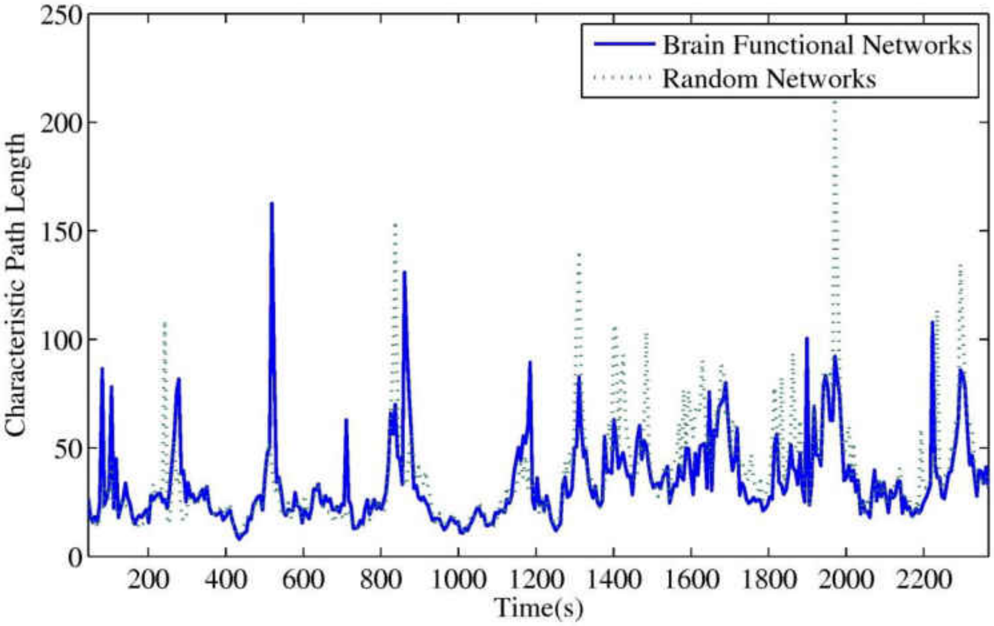


Figure 24. Characteristic Path Lengths of Brain Functional Networks and Similar Random Networks in the rested wakefulness condition

Small-world topology index was obtained as a ratio between gamma ratio of clustering coefficients and lambda ratio of characteristic path lengths. The values of index (δ_{RW}) are observed to fluctuate around its mean ($\bar{\delta}_{RW} = 1.9$) (see Figure 25). A t-test showed that the average of δ_{RW} was significantly higher than one in rested wakefulness (p<0.001), generally indicating the small-world topology of brain functional networks in the rested wakefulness condition.

The topology of brain functional networks was changing over time with the fluctuating index values. Specifically, brain functional networks showed small-world topology in most cases:

$$p_{RW} = \frac{number\ of\ windows\ with\ \delta_{RW}>1}{total\ number\ of\ windows} = \frac{283}{388} = 72.9\% \qquad (6.1)$$

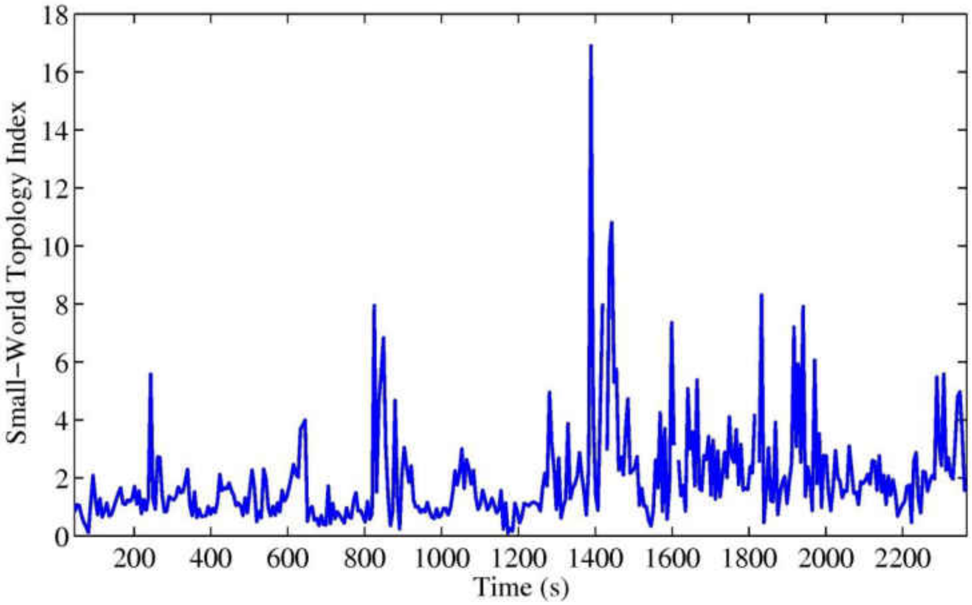


Figure 25. Values of Small-World Topology Index in the rested wakefulness condition

6.4.2 Small-World Topology Index in the chronic sleep deprivation condition

The average clustering coefficients of brain functional networks ($C_{net,SD}$) and the corresponding random networks ($C_{random,SD}$) in the chronic sleep deprivation condition are illustrated in Figure 26. The clustering coefficients of brain functional networks were significantly larger than those of similar random networks in the chronic sleep deprivation condition (p<0.001). The average clustering coefficient ratio (γ_{SD}) was larger than one in the chronic sleep deprivation condition.

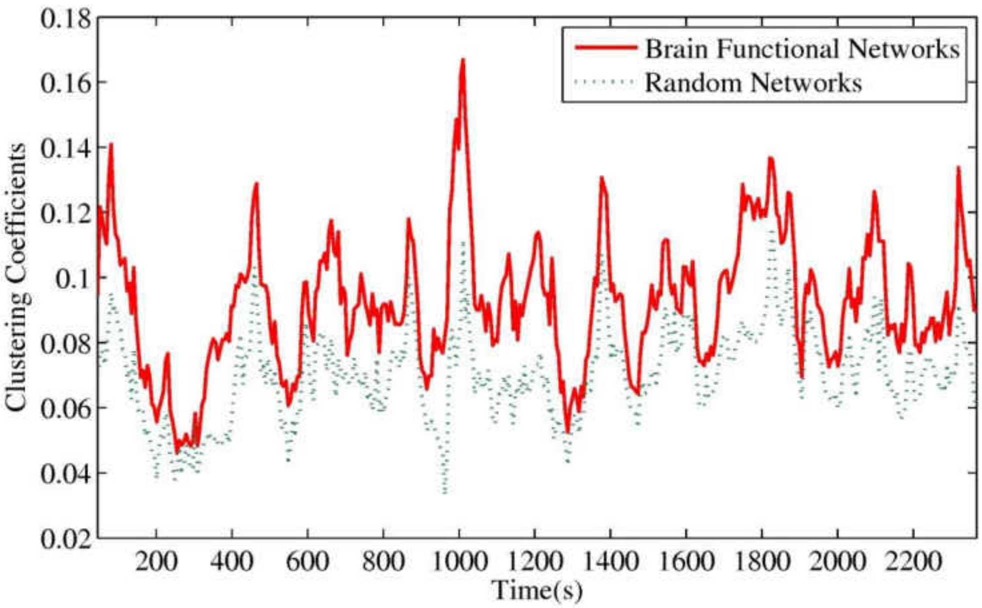


Figure 26. Clustering Coefficients of Brain Functional Networks and Similar Random Networks in the chronic sleep deprivation condition

The characteristic path lengths of brain functional networks ($L_{net,SD}$) and similar random networks ($L_{random,SD}$) under chronic sleep deprivation, were calculated and plotted in Figure 27. The results showed that brain functional networks had longer characteristic path lengths when compared with those of the random networks in chronic sleep deprivation. The average characteristic path length ratio (λ_{SD}) was larger than one in the chronic sleep deprivation condition.

The small-world topology index (δ_{SD}) of brain functional networks in the chronic sleep deprivation condition are illustrated in Figure 28. The values of δ_{SD} fluctuated with only a few cases where the value exceeded one:

$$p_{SD} = \frac{number\ of\ windows\ with\ \delta_{SD}>1}{total\ number\ of\ windows} = \frac{40}{388} = 10.3\% \tag{6.2}$$

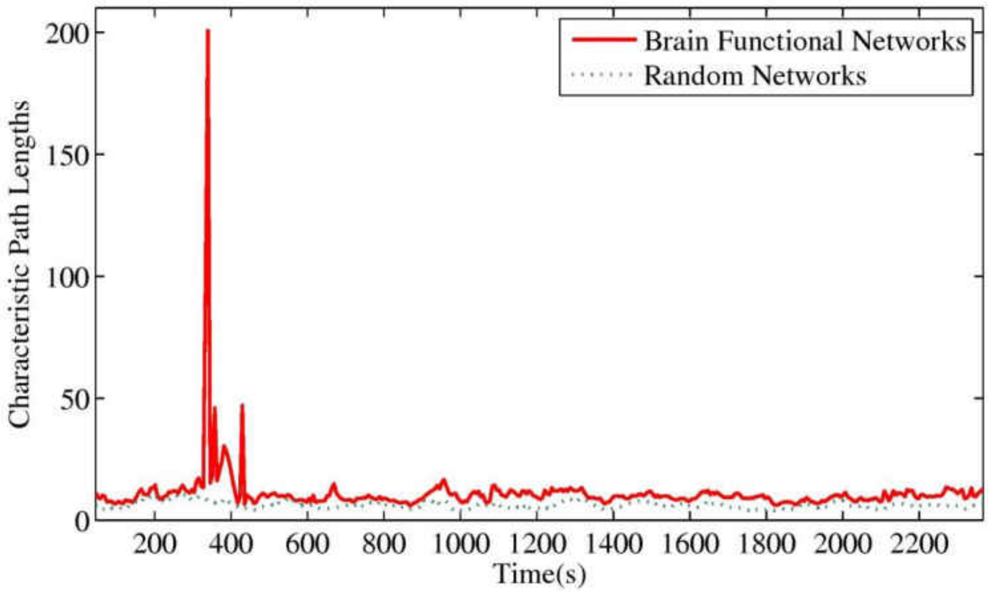


Figure 27. Characteristic Path Lengths of Brain Functional Networks and Similar Random Networks in the chronic sleep deprivation condition

In the rest of sliding-windows, the values of δ_{SD} were smaller than one. A t-test showed that the average of δ_{SD} was significantly smaller than one ($\bar{\delta}_{SD} = 0.8$) in the chronic sleep deprivation condition (*p*<0.001). This result indicated the random network topology of brain functional networks in the chronic sleep deprivation condition in general.

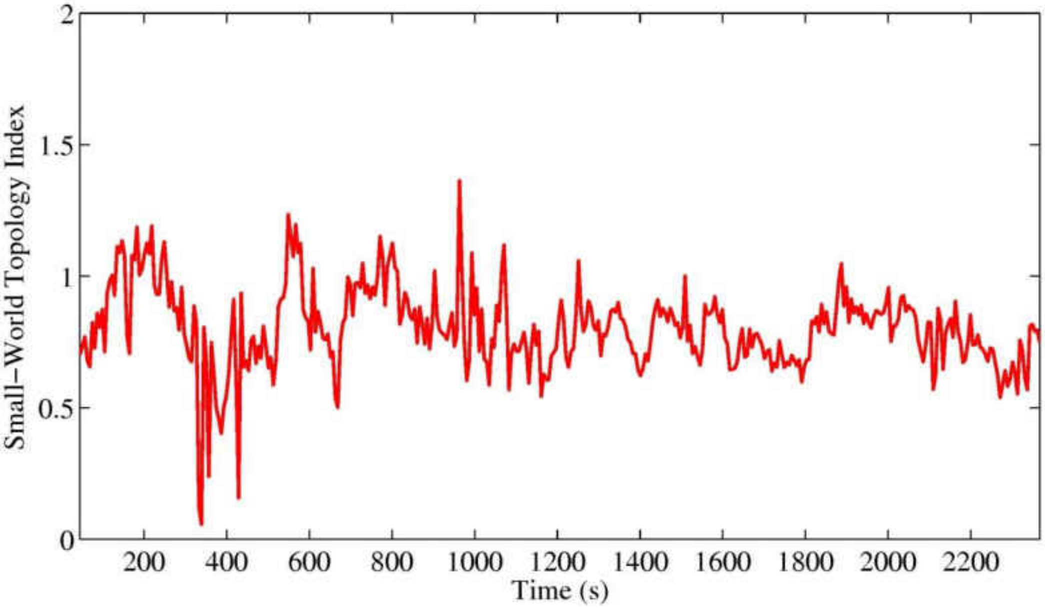


Figure 28. Values of Small-World Topology Index in the chronic sleep deprivation condition

CHAPTER 7: DISCUSSION

Partial least squares approach was applied to identify brain functional connectivity in both the rested wakefulness condition and the chronic sleep deprivation condition. With the integration of a sliding-window approach, the dynamic patterns of brain functional connectivity showed fluctuating connectivity strengths and changing structures of the brain network.

The results of graph theoretic analysis suggested a compensation mechanism between highly clustered organization and ineffective adaptability of the brain functional network in chronic sleep deprivation. Further, in the rested wakefulness condition the results indicated the dominance of small-world brain networks. However, such dominance was disrupted in the chronic sleep deprivation condition, indicating the ineffective adaptability of the brain functional network to maintain an optimal network topology.

7.1 Dynamic Patterns of Brain Functional Connectivity

Partial least squares approach has previously been applied by McIntosh et al. (2004) to fMRI data to determine the patterns of brain activity. In this thesis, the application of partial least squares approach was extended to determine the pattern of brain functional connectivity. Singular value decomposition was performed to distinguish brain activity or connectivity by experimental conditions, as illustrated in Figure 16. With the integration of a sliding-window approach, partial least squares approach had successfully identified dynamic patterns of brain functional connectivity in the rested wakefulness condition and chronic sleep deprivation condition. In addition, this approach further estimated brain functional connectivity as a weighted correlation coefficient. The weight of a given pair of brain functional connectivity indicated its reliability with the corresponding experimental condition.

The patterns of brain functional connectivity were observed to change dynamically (see Figure 18). Specifically, the strength measure of brain functional connectivity varied over time. Further, in some cases brain functional connectivity was not stable within a given experimental condition. For instance, Figure 19 illustrates that functional connectivity pair 39 is occasionally significant in the rested wakefulness condition, whereas sometimes is in the chronic sleep deprivation condition. Given different patterns of brain functional connectivity, the structures of the brain functional network were changing over time. This change can result from the adaption of brain networks to accomplish the attention task.

These observations demonstrated the non-stationary property of brain functional connectivity during sustained attention tasks in the chronic sleep deprivation condition, consistent with recent studies (Handwerker et al., 2012; Hutchison et al., 2013b; Kang et al., 2011; Kiviniemi et al., 2011; Li et al., 2014; Majeed et al., 2011). Specifically, the non-stationary property of brain functional connectivity included not only the fluctuating strengths of connectivity, but also the structure changes of functional connectivity. Thus, the dynamic patterns of brain functional connectivity can help to reveal more information of how chronic sleep deprivation impairs sustained attention.

7.2 Graph Theoretic Analysis of Brain Dynamic Functional Networks

Given the dynamic patterns of brain functional connectivity, graph theoretic analysis was performed to investigate the properties of brain dynamic functional networks using two network measures, i.e., clustering coefficient and characteristic path length.

The results showed that in the chronic sleep deprivation condition, brain functional networks had larger clustering coefficients when compared with those in the rested wakefulness condition, illustrating a highly clustered organization of brain functional networks (see Figure 21). This observation suggested that the human brain made more efforts to maintain sustained attention through utilizing more connections, as illustrated in Figure 20. Similarly, researchers have observed increased metabolism in some brain regions including the thalamus (Chee & Tan, 2010; Chee et al., 2008; Portas et al., 1998), anterior cingulate (Poudel et al., 2013) and frontal parietal cortex (Chee et al., 2008; Poudel et al., 2013; Weissman et al., 2006) in the chronic sleep deprivation condition.

On the other side, highly clustered organization may also result from the ineffectiveness of attentional inhibition in chronic sleep deprivation. Aron et al. (2014) have defined inhibition as the suppression of inappropriate responses and interfering memories during retrieval. It can be postulated that the brain fail to inhibit inappropriate reactions to visual stimuli under chronic sleep deprivation, resulting in a larger amount of brain connections. In terms of performance, ineffective inhibition may induce more response errors (i.e., lapses and errors) by failing to suppress incorrect responses. In addition, since the brain required more time to accumulate relevant information from excessive reactions, sleep-deprived subjects may have prolonged response time.

Characteristic path length of brain functional networks in the chronic sleep deprivation condition was significantly shorter than that in the rested wakefulness condition, indicating a shorter communication distance among brain regions (see Figure 22). This result was attributed to the highly clustered organization of the brain functional network in chronic sleep deprivation, which dramatically reduced the distance of communication between the distant regions. Given that characteristic path length is a widely used measure of global information integration, short characteristic path length may indicate fast response to sensory stimuli. Thus, the shorter characteristic path length of brain functional networks in chronic sleep deprivation was postulated to compensate for the effects of ineffective inhibitions, resulting in a non-significant increase of the average response times.

The variance of the clustering coefficient can be attributed to the dynamic patterns of brain functional connectivity, indicating an adaption of the human brain to accomplish a given task. From the perspective of brain functional networks, such an adaption represents the network's ability of achieving effective information synchronization through network reconfiguration. This is called the adaptability of brain functional networks. With an effective adaptability, the change of clustering coefficient of brain functional networks should effectively influence the characteristic path length. According to the results, in the sleep deprivation condition, the clustering coefficient of brain functional networks had large variances, resulting from disconnecting or reconnecting important connections with large weights (see Figure 21). However, the corresponding network characteristic path length has not changed significantly, indicating the ineffective adaptability of brain functional networks in the chronic sleep deprivation condition (see Figure 22). On the contrary, brain functional networks in the rested wakefulness condition showed an effective adaptability with small variance of the clustering coefficient, but also large variance of characteristic path length. In addition, the ineffective adaptability of brain functional networks in chronic sleep deprivation can result in instability of performance.

In the chronic sleep deprivation condition, highly clustered organization can compensate for the ineffective adaptability of brain functional networks to sustain attention. Previous studies have suggested the existences of similar compensation mechanics in the human brain. For instance, hyperactivation of the thalamus compensated for the deficits of parietal, indicating increased alertness effort in the sleep deprivation condition (Portas et al., 1998; Tomasi et al., 2009). In addition, another compensation mechanism was observed between increased activity in the fronto-parietal area induced by attentional lapses and less efficient perceptual processing (Weissman et al., 2006).

7.3 Dynamic Topology of Brain Functional Networks

The small-world topology index was calculated to investigate the dynamic topology of brain functional networks. In the rested wakefulness condition, the brain functional network showed the small-world topology during the sustained attention task, with the average small-world topology index larger than one (see Figure 25). The small-world brain network has been hypothesized to reflect an optimal network organization with a balance between information processing and global synchronization (Barabási & Albert, 1999; Bassett et al., 2009; Latora & Marchiori, 2001).

Further, in terms of dynamic brain functional networks, the index values kept fluctuating over time in the rested wakefulness condition as illustrated in Figure 25. Although in some cases brain functional networks exhibited the random network with index smaller than one, small-world topology of brain functional networks was presented in most of the cases. This observation demonstrated that the brain successfully maintained the dominance of small-world brain networks in the rested wakefulness condition. Such results further suggested the effective adaptability of brain functional networks to dynamically preserve the optimal network structure in the rested wakeful ness condition.

In the chronic sleep deprivation condition, brain functional networks exhibited the random network topology with the average index smaller than one. In general, the topology of brain functional networks was altered from the small-world network to the random network, with decreased local communication efficiency. Since the random network intended to connect nodes with equal probability regardless of the importance of the connection, such a structure can result from ineffective inhibition due to chronic sleep deprivation.

Further, previous studies have indicated that the alteration of small-world brain networks can be linked to several brain diseases (He et al., 2008; Micheloyannis et al., 2006; Rubinov et al., 2009; Sanz-Arigita et al., 2010; Stam et al., 2009; Stam et al., 2007b; Wang et al., 2009). For instance, attention-deficit/hyperactivity disorder (ADHD) is identified by developing inappropriate responses of excessive inattention, impulsivity, and/or hyperactivity (Xia et al., 2014). Studies have also demonstrated a disorder-related shift of the small-word networks to the regular networks, with increased local efficiency and decreased global efficiency (Wang et al., 2009; Xia et al., 2014). Alzheimer’s disease (AD) is indicated as a disconnection syndrome of brain functional networks (Delbeuck et al., 2003). The random brain functional networks in Alzheimer’s disease can be attributed to losing global information synchronization (Sanz-Arigita et al., 2010). The alteration of small-world brain networks to the random networks can contribute to the impairment of sustained attention in chronic sleep deprivation.

From the perspective of dynamic brain functional networks, in the chronic sleep deprivation condition, brain networks still show small-worldness in a few cases. In other words, whilst randomization, there still existed subtle small-world topology in the underlying brain network structure. This observation illustrated that chronic sleep deprivation disrupted the dominance of small-world brain networks, rather than totally altering it. Such results further indicated that in the chronic sleep deprivation condition the brain fails to maintain the dominance of small-world topology, which may result from the ineffective adaptability of brain functional networks.

7.4 Impaired Sustained Attention in the chronic sleep deprivation condition

The results of performance analysis demonstrated that chronic sleep deprivation can impair human sustained attention. Such results can provide evidence to support the observations of graph theoretic analyses, in terms of attentional performance.

A highly clustered organization of brain functional network in the chronic sleep deprivation condition may indicate the ineffectiveness of attentional inhibition (see section 7.2). The failure of attentional inhibition can increase the time that the brain needs to accumulate relevant information from excessive responses, resulting in a slower response speed. Furthermore, the inappropriate responses due to ineffective inhibition may also induce more responses errors. Such indications have been verified with the results of the performance analysis. Chronically sleep-deprived subjects had significantly lower response accuracy with more lapses, compared with those in the rested wakefulness condition (Table 2). The low response accuracy resulted from increasing attentional lapses and responses errors.

Attentional lapses described the slow responses of participants, usually with response times longer than 500ms (Weissman et al., 2006). Since the slowest 10% of response times represented the response times in the lapse domain (see Table 2), the prolonged slowest responses were consistent with the increasing number of lapses in chronic sleep deprivation. The lapses and slower response times have been related to the changes in cortical sensory, attentional and motor control pathways following sleep deprivation (Drummond et al., 2005b; Naito et al., 2000). Studies have shown that lapses may result from transient disruption of top-down attentional control during selective attention tasks in the rested wakefulness condition (Padilla et al., 2006; Weissman et al., 2006).

A shorter characteristic path length of brain functional networks has been observed in the chronic sleep deprivation condition. This observation suggests an efficient information integration resulting from a shorter communication distance under sleep deprivation. However, a highly clustered organization of brain functional networks due to ineffective inhibition may prolong the response times in the chronic sleep deprivation condition. The effects of these two opposite observations have been shown in the results of the performance analysis, that no significant differences of the response times has been found between the rested wakefulness condition and the chronic sleep deprivation condition.

Furthermore, an ineffective adaptability of brain functional networks has been revealed in the chronic sleep deprivation condition. With ineffective adaptability, the brain may fail to maintain the stability of attentional performance during the task. The results of the performance analysis showed the decreased stability with large variances of response times in the chronic sleep deprivation condition (Table 2). The ineffective adaptability of brain functional networks may result from the wake state instability, which described the competing effects between wake maintenance and sleep initiation (Dorrian et al., 2005; Durmer & Dinges, 2005; Lim & Dinges, 2008). Several brain neurons have been related to the shift from wake to sleep, including brain stem, hypothalamus, basal forebrain, and ventral lateral preoptic nucleus (Saper et al., 2001; Szymusiak et al., 2007). With the spread of the wake-sleep shift to cortical areas, distributed changes in brain activation have been observed in lapses during sleep deprivation (Chee et al., 2008).

In addition, the results of performance analysis also showed a significant decrease of response accuracy and slightly prolonged response time in chronic sleep deprivation, as shown in Table 2. These observations may indicate a speed-accuracy tradeoff mechanism in which chronically sleep-deprived subjects intended to maintain their response speed through scarifying their response accuracy. The speed-accuracy tradeoff has been described as a strategic adjustment in the decision-making process to adapt the environmental demands (Bogacz et al., 2010; Fitts, 1966; Wickelgren, 1977). The neural mechanism of the speed-accuracy tradeoff in chronic sleep deprivation requires further investigation.

CHAPTER 8: CONCLUSION

This thesis aimed to investigate the effects of chronic sleep deprivation on sustained attention from the perspective of dynamic functional connectivity. The experiment was conducted by Department of Cognitive Neuroscience and Neuroergonomics at Jagiellonian University, Krakow, Poland. A modified spatial cueing tasks was used to assess human sustained attention in both the rested wakefulness condition and the chronic sleep deprivation condition.

Performance analysis results demonstrated that chronic sleep deprivation can impair sustained attention, reflected by decreased response accuracy and increased attentional lapses. Variable performances, especially for response times with significantly large variance, indicated the instability of state in the chronic sleep deprivation condition. In addition, a speed-accuracy tradeoff mechanism was observed in which chronically sleep-deprived subjects intended to maintain response speed through scarifying the response accuracy.

Partial least squares approach was applied to identify brain functional connectivity in both the rested wakefulness condition and the chronic sleep deprivation condition. With the integration of the sliding-window approach, the dynamic patterns of brain functional connectivity were observed with fluctuating connectivity strengths and changing structures of brain networks. The functional connectivity was estimated as a weighted correlation coefficient, whose weight indicates its reliability with the corresponding experimental condition. The brain was then modeled as a series of dynamic functional networks in each experimental condition, whose nodes represented twenty segregated brain regions, and the edges represented the estimated functional connectivity. A graph theoretic analysis was used performed to investigate the dynamic properties of brain functional networks, using network measures of clustering coefficient and characteristics path length.

In the chronic sleep deprivation condition, a compensation mechanism between highly clustered organization and ineffective adaptability of brain functional networks has been observed, in order to maintain sustained attention. Specifically, a highly clustered organization of brain functional networks has been found with a large clustering coefficient. This organization suggests that the brain utilizes more connections to maintain attention in the chronic sleep deprivation condition. Smaller impact of clustering coefficient variation on characteristics path lengths has indicated an ineffective adaptability of brain functional networks.

In the rested wakefulness condition, brain functional networks showed the small-world topology in general, with the average small-world topology index larger than one. Small-world topology has been identified as an optimal network structure with the balance between local information processing and global integration. Given the fluctuating values of index over time, small-world brain networks have been observed in most cases, indicating an effective adaptability of the brain to maintain dominance of the small-world network in the rested wakefulness condition. On the contrary, given that the average small-world topology was index smaller than one, brain functional networks generally exhibit random network structure. From the perspective of dynamic functional networks, even though there were a few cases showing small-world brain networks, the brain has failed to maintain the dominance of small-world networks in the chronic sleep deprivation condition.

This thesis was the first to investigate the effects of chronic sleep deprivation on sustained attention from the perspective of dynamic brain functional connectivity. To the best of our knowledge, the proposed methodology was also the first application of partial least squares approach to identifying brain functional connectivity. The results have extended the current knowledge about the effects of chronic sleep deprivation in terms of dynamic brain functional networks. A compensation mechanism between highly clustered organization and ineffective adaptability of brain functional networks has been observed in the chronic sleep deprivation condition. Further, it was revealed that chronic sleep deprivation impairs sustained attention by reducing the effectiveness of brain functional networks' adaptability, resulting in the disrupted dominance of small-world brain networks.

In future work, regression analysis may be used to determine the relationship between cognitive performance measures and corresponding brain network measures. Such relationship may be different between the rested wakefulness condition and the chronic sleep deprivation condition, which can extend current understanding of the performance impairments due to sleep deprivation. In addition, other network measures (i.e., degree distribution) can be used to investigate the resilience of brain functional networks.

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