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A Short Window Granger Causality Approach to Identify Brain Functional Pattern Associated with Changes of Performance Induced by Sleep Deprivation

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A SHORT WINDOW GRANGER CAUSALITY APPROACH TO
IDENTIFY BRAIN FUNCTIONAL PATTERN ASSOCIATED
WITH CHANGES OF PERFORMANCE INDUCED BY SLEEP
DEPRIVATION

by

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ABSTRACT

The comprehensive effect of sleep deprivation on biological and behavioral functions largely remains unknown. There is evidence to support that human sleep must be of sufficient duration and physiological continuity to ensure neurocognitive performance while we are waking. Insufficient sleep would lead to high risk of human-error related to accidents, injuries or even fatal outcomes. However, in modern society, more and more people suffer from sleep deprivation because of the increasing social, academic or occupational demand. It is important to study the effect of sleep deprivation, not only on task performance, but also on neurocognitive functions. Recent research that has explored brain effective connectivity has demonstrated the directed inference interaction among pairs of brain areas, which may bring important insight to understand how brain works to support neurocognitive function.

This research aimed to identify the brain effective connectivity pattern associated with changes of a task performance, response time, following sleep deprivation. Experiments were conducted by colleagues at Neuroergonomics Department at Jagiellonian University, Krakow, Poland. Ten healthy young women, with an average age of 23-year-old, performed visual spatial sustained-attention tasks under two conditions: (1) the rest-wakeful (RW) condition, where participants had their usual sleep and (2) the sleep-deprived (SD) condition, where participants had 3 hours less sleep than their usual sleep, for 7 nights (amounting to 21 h of sleep debt).

Measures included eye tracking performance and functional magnetic resonance imaging (fMRI). In each condition, each subject's eye-position was monitored through 13 sessions, each with 46 trials, while fMRI data was recorded. There were two task performance measures,

accuracy and response time. Accuracy measured the proportion of correct responses of all trials in each session. Response time measured the average amount of milliseconds until participants gazed at the target stimuli in each session. An experimental session could be treated as a short window. By splitting long trials of fMRI data into consecutive windows, Granger causality was applied based on short trials of fMRI data. This procedure helped to calculate pairwise causal influences with respect to time-varying property in brain causal interaction. Causal influence results were then averaged across sessions to create one matrix for each participant. This matrix was averaged within each condition to formulate a model of brain effective connectivity, which also served as a basis of comparison.

In conclusion, significant effect of sleep deprivation was found on response time and brain effective connectivity. In addition, the change of brain effective connectivity after sleep deprivation was linked to the change of response time. First, an analysis of variance (ANOVA) showed significant difference for response time between the RW condition and the SD condition. No significant changes for accuracy were found. A paired t-test showed that response time was significantly shorter in sleep deprivation for the visual spatial sustained-attention task. Second, Granger causality analysis demonstrated a reduction of bidirectional connectivity and an increase of directed influences from low-level brain areas to high-level brain areas after sleep deprivation. This observation suggested that sleep deprivation provoked the effective connectivity engaged in salient stimuli processing, but inhibited the effective connectivity in biasing selection of attention on task and in maintaining self-awareness in day time. Furthermore, in the SD condition, attention at the visual spatial task seemed to be driven by a bottom-up modulation mechanism. Third, a relationship was found between brain effective connectivity with response time.

Decreases of Granger causal influences in two directions, from medial frontal lobe to sub cortical gray nuclei and from medial parietal lobe to sub cortical gray nuclei, were associated with shorter response time in the SD condition. Additionally, an increase of Granger causal influence from medial parietal lobe to cerebellum was associated with longer response time in the SD condition.

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AL	Automated Anatomical Labeling	LT	Lateral Temporal Lobe
AIC	the Akaike Information Criterion	MF	Medial Frontal Lobe
ANOVA	The Analysis of Variance	MIO	Medial and Inferior Occipital Lobe
BIC	the Bayesian Information Criterion	MP	Medial Parietal Lobe
CB	Cerebellum	MVAR	Multivariate Autoregressive (Model)
CR	Central Region	NREM	Non-rapid Eye Movement Sleep
DMN	Default Mode Network	ROIs	Region-of-Interests
EEG	Electroencephalography	RW	Rest-wakeful (condition)
FDR	False Discovery Rate	SC	Sub Cortical Gray Nuclei
GCM	Granger Causality Mapping	SD	Sleep-deprived (condition)
LF	Lateral Frontal Lobe	TAL	Talairach Daemon
LO	Lateral Occipital Lobe	TSD	Total Sleep Deprivation
LP	Lateral Parietal Lobe	VAR	Vector Autoregressive (Model)

INTRODUCTION

The comprehensive biological and behavioral functions of sleep remain largely unknown. Human sleep must be of a certain length and endurance to ensure coherent levels of neurocognitive performance while we are awake (Banks & Dinges, 2007; Durmer & Dinges, 2005; Lim & Dinges, 2008). Siegel (Siegel, 2003) hypothesizes that 6-hour sleep is adequate to maintain waking cognitive functioning and other sleep beyond the core duration is optional. However, current studies have shown inconsistent result with this core sleep hypothesis. Van Dongen et al. (H. P. A. Van Dongen, Maislin, Mullington, & Dinges, 2003) found that sleep restriction between 4h and 6h for 14 days led to impaired neurocognitive performances comparable to those found under conditions of 1 to 2 days of total. Furthermore, instead of 6 hours, a threshold of sleep duration to prevent cumulative neurobehavioral deficits was estimated as 8.16 hours per 24 hours. This is consistent with the result from former study that sleep deprived individual needs 8 to 9 hours extended sleep to recovery. (Roehrs, Shore, Papineau, Rosenthal, & Roth, 1996).

Average nocturnal sleep time has been reported as 6.7 hours during weekdays and was 7.4 hours on weekends (Breslau, Roth, Rosenthal, & Andreski, 1997). Also, the overall population of adults that was affected by insufficient sleep has been estimated to be 20% in 2001 (Hublin, Kaprio, Partinen, & Koskenvuo, 2001). and increased to 35% in 2009 in epidemiological surveys, which is less than 7 hours per night ("Insufficient Sleep Is a Public Health Epidemic," 2013).

Sleep deprivation is part of our lifestyle because of increasing social, academic, and occupational demands (Bonnet & Arand, 1995). Young adults sacrifice their sleep time to finish work or school assignments, to maintain a social life with friends, to take care of their young children, or just to have time to do exercises. Older people largely suffer from insufficient sleep caused by aging-related sleep disorders. For some people, working at night or under sleep deprivation is a basic occupational requirement. Examples include law enforcement, pilots, medical school students, truck drivers and shift workers. All perform critical tasks often with insufficient sleep.

Sleep deprivation increases the risk of error related accidents (Dinges, 1995). Based on Dinges and Kribbs's framework (Dinges & Kribbs), the behavioral effect of sleep deprivation includes lapsing, cognitive slowing, memory effects, time-on-task effects and task-criterion response shifts. Studies also have shown that neurocognitive consequences of sleep deprivation include waking instability (Durmer & Dinges, 2005), increased daytime sleep propensity (Kribbs & Dinges, 1994), decreased cognitive speed/accuracy (Banks & Dinges, 2007; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008), degraded working memory tasks (Banks & Dinges, 2007; Chee & Chuah, 2007; Chee & Tan, 2010; Chee et al., 2008; Habeck et al., 2004; Padilla, Wood, Hale, & Knight, 2006), and increased attentional lapses (Banks & Dinges, 2007; Lim & Dinges, 2008). Behavioral variability involves errors of omission, errors of commission and time-order errors. Errors of omission refer to failures to respond to stimuli with respect to time. Errors of commission refer to incorrect response. As in visual spatial attention task, error of commission represented wrong direction, wrong location or responses when no stimulus is present (Fafrowicz et al., 2010).

Such neurocognitive and behavioral changes may bring injuries or even fatal outcomes, especially in occupations with requirements of noctural shift and long duration of operations. Financial lost from accidents induced by sleep deprivation have been estimated as $43 to $56 billion annually(Leger, 1994). Remarkably, the risk of exposure to accidents associated with fatigue and sleepness among motor vehicle riders has been commonly underestimated (Horne & Reyner, 1999; McCartt, Ribner, Pack, & Hammer, 1996)

Studying both neurocognitive and behavioral ramifications of sleep deprivation can lead to further understanding of behavioral consequences and can bring insight into neurocognitive mechanisms. Such developments would allow interventions to be developed that could alleviate the bad influence of sleep deprivation.

This research was organized as follows. Chapter 1 presented the existing literature of related fields with this research. Such topics included: (1) the effect of sleep deprivation, (2) neurocognitive model of attentional control and its links to brain structural model, (3) functions of the brain and (4) Granger Causality as a means to measure brain causal interactions.

Chapter 2 presented an overview of this research: (1) Research Gaps, (2) the objective of this research, followed by primary research problems, (3) an outline of a three-phase research methodology. Further details of studies at phase I, II and III would be given in Chapter 4-6, respectively, where each chapter summarized (1) the analysis procedures, (2) results and (3) discussions that were part of each particular research problem.

Chapter 3 demonstrated experiment data used in this research. Experiments were conducted by Dr. Fafrowic and her colleagues at Poland. Descriptions of experiment design and experiment measures were presented to support understanding of results. Chapter 7 concluded the answers addressed to each research problems and the contribution of this research.

CHAPTER 1: LITERATURE REVIEW

1.1 <u>Sleep Deprivation</u>

A survey of the current Analysis of the literature has suggested three general categories of studies. First, total sleep deprivation refers to continuous sleep restriction more than 45 hours in duration. Second, short-term total sleep deprivation refers to sleep restrictions up to 45 hours (less than and equal to 45 hours). Third, partial sleep deprivation, also known as chronic sleep deprivation, refers to sleep restriction less than 7 hours in every 24 hours. Duration of chronic sleep restriction studies generally last over one week (Durmer & Dinges, 2005). Table 1 shows a summarized category of sleep deprivation.

Table 1 Sleep Deprivation Category

Type of Sleep Deprivation	Sleep Loss	Duration
Total Sleep Deprivation	> 45 hours	Once
Short-term Total Sleep Deprivation	≤ 45 hours	Once
Chronic Sleep Deprivation	Less sleep than 7 hours per 24 hours	Over 7 Days

Drake (Drake et al., 2001) demonstrated that total sleep deprivation resulted in greater neurobehavioral deficits than the same amount of sleep loss accumulated through multiple nights of sleep restriction. However, well-controlled sleep-does-response experiments revealed that chronical sleep loss between 3 hours and 7 hours per 24 hours, accumulating for duration of 1-2 weeks leaded to near-linear decline in behavioral

alertness and cognitive performance (H. P. A. Van Dongen et al., 2003). Moreover, cumulative performance deficits in vigilance task induced by chronically restricted sleep over 14 days were comparable to those developed through even the most severe total sleep deprivation (64-88 hours) (Van Dongen et al., 2003). Such observations indicated that total sleep deprivation and chronic sleep deprivation were modulated by different regions and neuronal systems. Addionally, recovery from chronic sleep deprivaiton was reported to require longer time than from total acute sleep deprivaiton (Basner, Rao, Goel, & Dinges, 2013). Considering the habitable phenomena of chronic sleep deprivation in modern society and the servirity of its cumulative effects, it's more important to study the impact of chronic sleep deprivaiton.

1.2   Attentional Control

1.2.1   Goal-Directed and Stimulus-Driven Attentional Control

In everyday life, our attention is either consciously directed to or automatically attracted to a particular field or aspect of environment, such as to a specific sound or a certain location in visual place (Purves, 2008). The former is known as endogenous attention and the latter is exogenous attention. Endogenous attention is controlled by top-down cognitive modulation to visual areas in order to reach an expectation or accomplish a goal. Exogenous attention is driven by bottom-up sensory simulation involuntarily, especially by those novel or task-related stimulus. The dynamic interaction between these two system formulate where, how and what we pay attention to (Bressler, Tang, Sylvester,

Shulman, & Corbetta, 2008; Corbetta & Shulman, 2002; Fafrowicz et al., 2010; Purves, 2008).

A cognitive model involved with both endogenous (top-down) and exogenous (bottom-up) attentional control, summarized based on literature review, is shown in Figure 1. There are four difference processes: orienting, maintain orientation, detecting and reorienting. Orienting refers to selective process of sensory information, including aligning sensory processing system with the input channel, and biasing the processing of incoming visual input based on advanced information of the target's feature, such as a certain color, shape or spatial location (Corbetta & Shulman, 2002; Posner, 1980; Vecera & Rizzo, 2003). Then, working memory involves to store those advanced information online as active sensory representation for effective executive function in the absence of impending stimulation (Posner, 1980; Purves, 2008). It includes maintenance process and retrieval process. These advanced information benefit efficiency of attentional detection , but maintaining the information in memory is heavily relying on the sustained attending to the location (Awh & Jonides, 2001). Next, detection means a response movement to the target, such as saccadic eye movement or press a button, in order to report the existence of stimuli. These three processes formulate a goal-directed modulated by internal cognitive signals through the top-down attention system. In addition, our attention will be influenced by exogenous stimuli in the process of searching behaviorally relevant events. Salient and unattended peripheral stimuli catch human attention automatically without affection by working memory task (Corbetta & Shulman, 2002; Vecera & Rizzo, 2003), resulting in attention shift. This is a stimuli-driven attention control modulated by exogenous system.
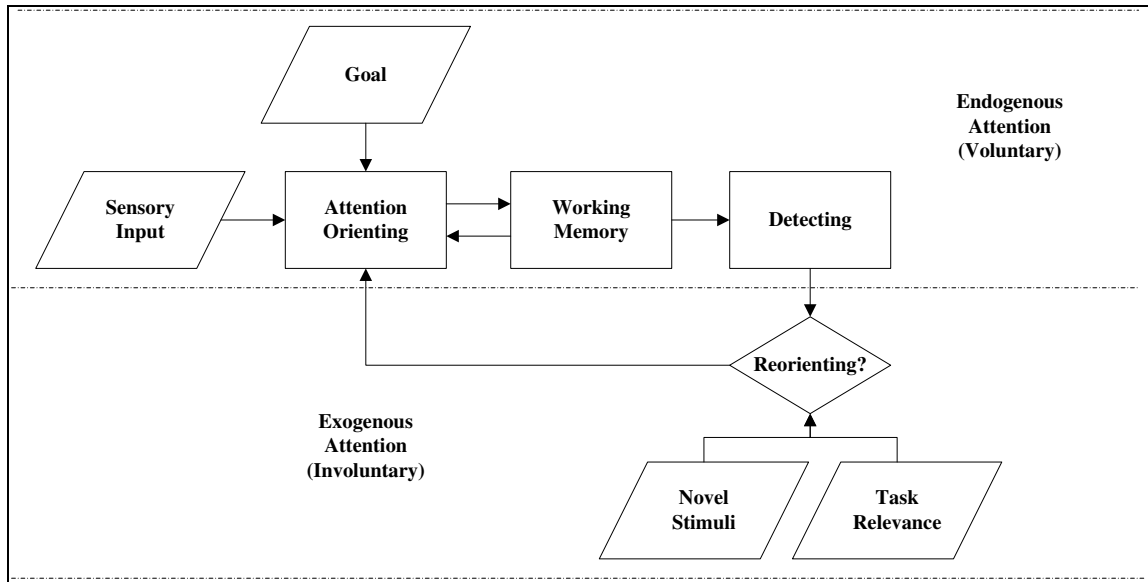
Figure 1 Attention Control Cognitive Model

Typically, human produce better performance with the knowledge of where a stimulus will occur in a complex visual field. This type of information is presented as a cue in experimental environment. It's well-studied about the benefits of valid cues, which provide correct predication about target's features or about task's expectancy. However, invalid sensory cues can yield a prolonged inhibition of attentional processing, resulting in worse performance compared with no-cue condition, which is known as inhibition of return (IoR), especially with the involvement of peripheral cue. Difference between the effect of valid cue and invalid cue reveals differentiated function of goal-directed attentional control and stimuli-driven attentional control (Müller & Rabbitt, 1989; Posner & Cohen, 1984).

1.2.2 Attentional Control Networks

Human fMRI studies (Bressler et al., 2008; Corbetta & Shulman, 2002; Vossel, Weidner, Driver, Friston, & Fink, 2012) have revealed that attention is modulated by two partially segregated neural networks dynamically. Dorsal frontalparietal network, consisting of bilateral intraparietal sulcus and frontal eye field, controls endogenous attention, directing voluntary attention, facilitation of visual cortex in preparation for impending event, and selecting response movement. Right-lateralized ventral frontalparietal network, including both temporoparietal junction and ventral frontal cortex at the right hemisphere, modulates exogenous attention, deploying attention to salient and unattended stimulation automatically and facilitating the detection of task-related and novel stimuli. Corbetta and colleagues's model demonstrated this attentional control mechanism, shown in Figure 2. FEF, IPS, TPJ and VFC referred to frontal eye field, intraparietal sulcus, temporoparietal junction cortex and ventral frontal cortex, respectively.

Several researches demonstrated supportive evidence to the involvement of parietal and frontal regions in attentional control. Corbetta and his colleagues (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000) observed a sustained activation of frontal and parental regions when subjects gazed their attention on the cue stimuli. In addition to selecting stimuli and orienting attention, dorsal frontal parietal network might be related to produce eye movement to the target stimuli as well. Frontal eye field modulated visual inputs processing and response movement programming. Together these results elicited

that the primary function of dorsal frontoparietal network was to orient attention to selective sensory input and to report detection through response movement.
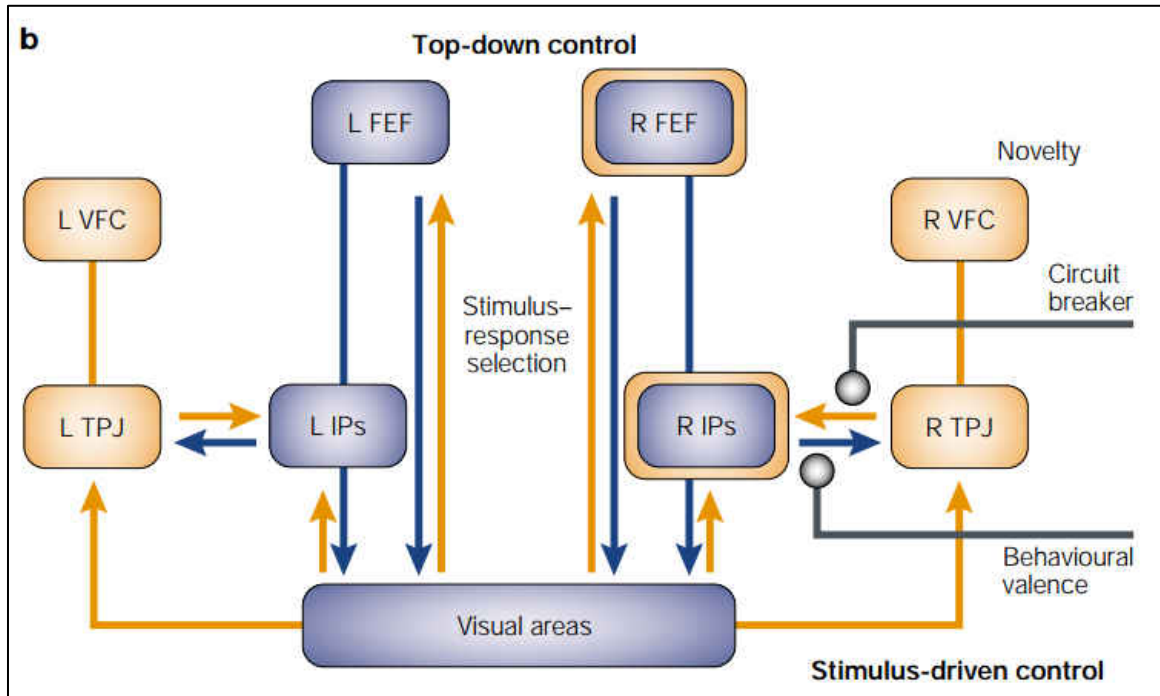
Figure 2 Neural Attentional Control Systems (Corbetta & Shulman, 2002)

Other than bilateral dorsal prefrontal network, ventral frontal parietal network was found strongly activated at the right hemisphere during the detection of salient and unexpected stimuli, especially of task-relevant stimuli that are outside attentional focus (Corbetta & Shulman, 2002). Recent study demonstrated that unattended stimuli attracted attention automatically and they disrupted ongoing task more effectively when they were relevant to behavioral objective or task, representing similar features to the target stimuli (Folk, Remington, & Johnston, 1992) or serving as targets in previous sessions (Bichot & Schall, 1999). Strong activation was observed at right temporoparietal junction cortex when target occurred at an unexpected location (Arrington, Carr, Mayer, & Rao, 2006).

Also, a meta-analysis (Corbetta & Shulman, 2002) of activation during the detection of low-frequency events showed sustained activation in a network consisting of temporoparietal junction cortex and ventral frontal cortex. However, novel stimuli might activate more robustly prefrontal regions (Clark, Fannon, Lai, Benson, & Bauer, 2000; Kiehl, Laurens, Duty, Forster, & Liddle, 2001). In addition, damage to right prefrontal regions specifically impaired detection of low-frequency events and novel stimuli (Daffner et al., 2000; Knight & Scabini, 1998). These evidences reflected that temporoparietal junction cortex and ventral frontal cortex might play different role in stimuli-driven attentional modulation. Together, the primary function of right-lateralized ventral frontal cortex was to evaluate distinct stimuli and reorient attention to those with potential to bring more behavioral benefits.

Through Granger causality analysis, directed influences were discovered between BOLD signals and represented directed interaction between different regions in attentional control (Granger, 1969; Roebroeck, Formisano, & Goebel, 2005). Several Granger causality studies revealed that bilateral frontal eye field to IPS exert top-down modulation to visual occipital cortex during visual attentional tasking (Bressler et al., 2008; Vossel et al., 2012). New research revealed that ventral network played a different role than dorsal network in visual attention. When invalid involved in visual attention task, there was a great Granger causality influence from visual cortex through frontal parietal systems, and at last back to frontal eye field (DiQuattro & Geng, 2011). This elicited that ventral network modulated bottom-up sensory pushing mechanism to suppress dorsal network's influence in top-down modulation.

1.3   <u>Function of the Brain</u>

This section presented how brain works at rest state and under sleep deprivation, and additionally, how to measure persistent brain functions was demonstrated.

1.3.1   The Brain at Rest

A distinct network of brain regions was observed representing baseline state at rest, indicating the existence of a "default mode network" (DMN) (Raichle et al., 2001; Shulman et al., 1997). Such network demonstrated a reduction of activation cognitive tasks and anti-correlated with task-related executive functional regions. Greicus and his colleagues (Greicius, Krasnow, Reiss, & Menon, 2003) provided the first evidence of DMN's existence by demonstrating functional connectivity between brain regions at brain resting state. Repeated observations showed that ventromedial prefrontal cortex, posterior cingulate cortex, ventral anterior cingulate, lateral temporal cortex, left inferior parietal cortex and hippocampal formation were main regional nodes in DMN and the first two played key roles. (Buckner, Andrews-Hanna, & Schacter, 2008; Esposito et al., 2006; Fransson, 2006; Greicius et al., 2003; Gusnard, Akbudak, Shulman, & Raichle, 2001; Mckiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Raichle et al., 2001). The anticorrelated system included the frontal eye fields, intraparietal sulcus, middle temporal region, supplementary motor area, temporoparietal junction, dorsolateral prefrontal cortex and insula (Fox, Snyder, Zacks, & Raichle, 2005).

Even though they were highly coupling during task and at rest, elements in DMN negatively correlated to very different networks. posterior cingulate cortex was found

anticorrelated with prefrontal and parietal regions (Uddin, Clare Kelly, Biswal, Xavier Castellanos, & Milham, 2009), which involved in sensory processing and motor control functions (Hampson, Peterson, Skudlarski, Gatenby, & Gore, 2002; Uddin et al., 2009), while ventromedial prefrontal cortex was negatively correlated with lateral parietal visual spatial and temporal attention networks (Uddin et al., 2009). Another Granger causality study showed greater influence exerted from posterior cingulate cortex and ventromedial prefrontal cortex to their anitcorrelated networks than the other way around. Additional behavioral evidence showed that increased activation was found in visual cortex, while little changed of connectivity pattern was found in posterior cingulate cortex during a visual attention task and resting state. DMN was minimally disrupted by sensory processing tasks with limited cognitive.

Reduced activation of DMN during goal-directed task indicated an inhibition interaction with those task-oriented brain regions at rest. Moreover, the antagonistic relationship between DMN and their anti-correlated networks revealed the modulation of DMN on goal-directed brain regions, suppressing executive function or sensory processing of exogenous stimuli, maintaining attentional focus on current task and shifting attention based on task requirements. Together, DMN was essential neural structure serving in dynamic modulation of goal-directed task performance.

1.3.2   Brain under Sleep Deprivation

A lot of researches have been conducted about the impact of sleep deprivation on working memory, sustained attention and visual spatial attention through different tasks

(Chee & Choo, 2004; Chee & Chuah, 2007; Drummond, Gillin, & Brown, 2001; Habeck et al., 2004). Those studies revealed special brain activation patterns of changes in cerebral blood flow post sleep deprivation, indicating the neuronal mechanisms provoked by sleep deprivation and contributing to performance deficits.

Decreased activation pattern has been observed in parietal lobes(Chee & Choo, 2004; Chee & Chuah, 2007; Chuah, Venkatraman, Dinges, & Chee, 2006; Habeck et al., 2004), temporal lobes (Habeck et al., 2004), occipital lobes(Habeck et al., 2004), extrastriate cortex(Chee & Chuah, 2007), posterior parietal cortex (Chee & Chuah, 2007) and introparietal sulcus (Chee & Chuah, 2007). Increased activation pattern has been found in thalamus (Chee & Choo, 2004; Habeck et al., 2004) and frontal lobes (Drummond et al., 2001; Habeck et al., 2004).

Generally, different activation patterns have linked to the changes in neurocognitive modulation. Increased activation refers to compensatory mechanism. Decreased activation is associated with dysfunction and performance impairment.

- Increased Activation: compensatory mechanism
- Decreased Activation: dysfunction

Studies also demonstrated contradictory findings: two studies (Chee & Choo, 2004; Habeck et al., 2004) reported increased thalamic activation, while the other (Chuah et al., 2006) reported decreased thalamic activation. On the other hand, several studies (Chee & Choo, 2004; Chee & Chuah, 2007; Chuah et al., 2006; Habeck et al., 2004) showed decreased activation in parietal lobes, while one showed increased parietal

activation (Chee & Choo, 2004). Such different observations could be supportive evidence about the complexity of brain activities under sleep deprivation.

Brain is a complex system. Different brain regions interact with each other and dynamically modulate cognitive functions to accomplish task goals or shit attention to distinct stimulations. In addition, even though contradictory findings exist, it reveals that the distinct neuronal systems where those regions belong to differentially playing important roles in neurocognitive control. Those systems include attentional control network, default-mode network, subcortical regions and executive-function-related regions. Here is a summary of key regions in different neurocognitive systems, shown in Table 2.

Current studies also showed a reduced deactivation patterns in regions belonging to a default-mode network (DMN) (Chee & Chuah, 2007). A reduced deactivation pattern could be observed as an increased activation pattern without comparing with the control state (pre sleep deprivation state) (Chee & Choo, 2004). Regions, representing reduced activation patterns following sleep deprivation, include posterior cingulate cortex (Chee & Chuah, 2007), medial prefrontal cortex (Gujar, Yoo, Hu, & Walker, 2010) and inferior parietal lobule (De Havas, Parimal, Soon, & Chee, 2012). Deactivation patterns during task demonstrated that this network ongoing at rest and suspended during goal-oriented task. Reduced-deactivation pattern refers to reduced inhibition control. Inhibition control enables biasing selection of task-relevant information, goal-oriented attentional focus and suppress of response to distinct stimulation.

- Reduced Deactivation (Increased activation): reduced inhibition control

Studies investigating the effect of sleep deprivation on internal connectivity within DMN and on their links to the anticorrelated network have attracted more attention. Experiments were carried out with a focus on oriented cognitive function, such as attention, working memory and executive function (De Havas et al., 2012). Reduced correlation in functional connectivity of DMN and anticorrelated network was reported under sleep deprivation (De Havas et al., 2012; Gujar et al., 2010; Sämann et al., 2010). Also, altered DMN regional function may be related to intrinsic impairment following sleep deprivation (De Havas et al., 2012) based on a new discovery of a double association relationship between task-related reduced deactivation and reduced connectivity within DMN, mainly in anterior and posterior midline regions (Gujar et al., 2010). This is supported by coupling occurrence of reduced DMN connectivity and reduced deactivation pattern (Chee & Choo, 2004; Chee & Chuah, 2007; De Havas et al., 2012). In addition, anticorrelation of networks in the resting state may be related to segregation of neuronal processes serving exogenous attention driven by external stimuli and endogenous attention directed by task objectives (Fox & Raichle, 2007). Altered anticorrelation may refer to shifting attentional focus from current goal to external sensory processing.

Table 2 Key Regions in Attention Related Networks

Network	Regions
Dorsal frontalparietal network	Intraparietal sulcus
	Frontal eye field
Right-lateralized ventral frontalparietal network	Temporoparietal junction
	Ventral frontal cortex
Default-mode network (DMN)	Posterior cingulate cortex
	Ventral anterior cingulate cortex
	Medial prefrontal cortex
	Inferior parietal cortex
	Lateral temporal cortex
Executive function system	Dorsal-lateral prefrontal cortex
	Ventromedial prefrontal cortex
	Posterior parietal cortex
	Anterior cingulate cortex
Subcortical system	Basal ganglia
	Thalamus

1.3.3   Measure of Brain Functions

The study of measuring brain functions involves two topics: brain functional segregation and brain functional integration. Functional segregation is a study about functional specialization within an anatomically segregated cortical area (Friston, 2011). Functional segregation is evolved from the notion of brain functional localization that each brain region performs a specific cognitive function. However, such functional model can't explain the complexity of brain modulation. Instead, the neurocognitive and behavioral performance is a result of complex interactions among spatially segregated brain areas.

Functional integration focuses on such interaction of activated brain areas (Friston, 2011). There are two ways to analyze functional integration. First, functional connectivity measures unidirectional connectivity, estimated by the temporal correlation between spatially remote areas (Friston, 1994). Second, effective connectivity measures directed influence that one neural system exerts over another estimated by temporal precedence relationship (Friston, 2011).

1.4   <u>**Granger Causality**</u>

Granger causality is one of the most widely used methods to analyze effective connectivity between brain regions based on their temporal precedence. Its basic idea, introduced by Wiener (Wiener, 1956), is that time series X Granger causes time series Y if including Y's past information improves the prediction of future values of X. The first practical implementation of Wiener's idea is formulated by Clive Granger (Granger, 1969)

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to predict time series of stock market. He was awarded the Nobel Memorial Prize in Economic Sciences in 2003.

Applying Granger causality to measure the brain effective connectivity between pairs of brain areas, X_t and Y_t represent time series of Blood-oxygen-level dependent (BOLD) hemodynamic responses in two brain regions, collected via functional magnetic resonance imaging. Brain region X exerts Granger causal influence to brain region Y only if knowledge of past time series of BOLD responses of Y improves prediction of the current BOLD responses of X even when the past history of X is included in the predictive model (Deshpande, LaConte, James, Peltier, & Hu, 2009; Roebroeck et al., 2005).

Granger causality has become a popular method to investigate brain effective connectivity in neural applications and many statistical methods have been proposed as an extension of the traditional Granger causality. The following sections would introduce the basic concept of a few Granger causality methods and their mathematical frameworks, in the sequence of class Granger causality, conditional Granger causality, partial Granger causality, multiple realizations Granger causality and spatial-temporal Granger causality. An overview of these methods was shown in Table 3.

Table 3 An Overview of Granger Causality Methods

Methods	Reference	Features
Classic Granger Causality	(Geweke, 1982; Granger, 1969)	Analyze directed causal influence between two brain areas
Granger Causality Mapping	(Roebroeck et al., 2005)	Explore causal influence flow between one region of interest and all other brain areas
Conditional Granger Causality	(Ding, Chen, & Bressler, 2006)	Exclude the influences from spurious connections, when estimating causal interactions between two brain areas
Partial Granger Causality	(Guo, Seth, Kendrick, Zhou, & Feng, 2008)	Eliminate the influences from exogenous inputs and latent variables in addition to spurious connections, when estimating causal interactions between two brain areas
Multiple Realizations Granger Causality	(Ding, Bressler, Yang, & Liang, 2000; Ding et al., 2006)	Analyze causal interactions when data are in the form of multiple realizations
Spatial-Temporal Granger Causality	(Luo et al., 2013)	Provide better measures of dynamic causal structure

1.4.1   Classic Granger Causality

Consider X_t and Y_t are two stochastic processes. Granger causal influence between them can be measured as a linear dependence (Geweke, 1982) via vector autoregressive (VAR) model. Each process is represented as restricted VAR models:

$$X_t = \sum_{j=1}^{p} a_1 X_{t-j} + \varepsilon_{1t}, \ \ var(\varepsilon_{1t}) = \Sigma_1$$

$$Y_t = \sum_{j=1}^{p} b_1 Y_{t-j} + \eta_{1t}, \ \ var(\eta_{1t}) = \Gamma_1$$

where p is maximum number of lagged observations, which is also known as model order (Ding et al., 2006).

To analyze whether Y_t Granger causes X_t, an unrestricted prediction model of X_t, jointing with Y_t, is represented as:

$$X_t = \sum_{j=1}^{p} a_2 X_{t-j} + \sum_{j=1}^{p} b_2 Y_{t-j} + \varepsilon_{2t}, \ \ var(\varepsilon_{2t}) = \Sigma_2$$

where the noise terms are uncorrelated over time.

Based on (Geweke, 1982), the measure of linear inference between X_t and Y_t can be defined as:

$$F_{Y \rightarrow X} = \ln \frac{\Sigma_1}{\Sigma_2}$$

where $F_{Y \rightarrow X}$ can never be negative. If $F_{Y \rightarrow X}$ equals to zero, time series Y_t has no causal influence with time series X_t, hence brain region X is independent to brain region Y in the context of neural applications. A ratio larger than zero refers to the existence of effective connectivity.

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The establishment of VAR model requires the estimation of model order p. A principled means to determine model order is to minimize a criterion that balances a good representation of the data and good model estimation (Bressler & Seth, 2011; Seth, 2010). One criteria is the Akaike information criterion (Akaike, 1974), which is defined as

$$AIC\ (p) = \log|\Sigma| + \frac{2n^2 p}{T}$$

An alternative criteria is the Bayesian information criterion (Schwarz, 1978), which is defined as

$$BIC\ (p) = \log|\Sigma| + \frac{n^2 p \log T}{T}$$

where T represents the number of total time series data observed through all trials and n represents the number of variables. BIC is commonly used in neurocognitive research since it can compensate for the large number of data points and may have a better performance (Ding et al., 2006). The computation of regression coefficients in the VAR model can be implemented via the ordinary-least-squares (Seth, 2010). In addition, the estimation of VAR model requires the time series to be zero mean. Thus, the temporal mean should be subtracted from the entire time series.

Statistical significance of F, the Granger causal influence, can be determined via classic comparison of regression models based on the extra sum of squares principle (F test) (Greene, 2003):

$$H_0: \varepsilon_{1t}{}^2 = \varepsilon_{2t}{}^2$$
$$H_a: \varepsilon_{1t}{}^2 > \varepsilon_{2t}{}^2$$

$$F = \frac{\frac{RRSS - URSS}{p}}{\frac{URSS}{T - p - 1}}$$

where RRSS is the Residual Sum of Square of the restricted VAR models and

URSS is the Residual Sum of Square of the unrestricted VAR models. T is the total

number of trials used to estimate the unrestricted model. The F-statistic approximately

follows an F distribution with degrees of freedom p and T-p-1. The null hypothesis is

there is no difference of prediction between restricted model and unrestricted model. We

reject the null hypothesis if F-statistic is larger than significance threshold. Therefore we

conclude that the unrestricted model provides a better predication than does the restricted

model and Y Granger causes X.

1.4.2   Granger Causality Mapping

Granger causality was first applied based on fMRI data by Goebel (Goebel,

Roebroeck, Kim, & Formisano, 2003). Then Roebroeck (Roebroeck et al., 2005)

extended Goebel's methods to a Granger causality mapping (GCM) approach to explore

effective connectivity between any pair of two brain areas over the entire brain. This

approach was useful to formulate structural model of regions and their directed

interactions, especially when hypotheses of inference relationships among brain areas

were sensitive to preselected structural model or were not readily available at the current

stage of research. However, this approach couldn't distinguish the influence of spurious

connections. If single connections exist in the directions from A to B and from A to C,

then it's highly likely that the connection from A to C will be selected. Thus, GCM may result in an ambiguous effective connectivity network due to its high density.

1.4.3   Conditional Granger Causality

As described in the section above, for three or more simultaneous time series, the inference relationship between any pair of the series may be directed or mediated by another one. Conditional Granger causality (Ding et al., 2006) is invented to address the issue of spurious interactions. By including other relevant time series in multivariate autoregressive (MVAR) model estimation, conditional Granger causality explicitly removed the misleading spurious interactions when measuring the causal influences between two time series. The ability of conditional Granger causality heavily relies on the incorporation of all other relevant information in the MVAR model estimation. However, this situation is very difficult to meet in reality due to the influences from both environmental inputs and latent variables (Camacho & Collins, 2009).

1.4.4   Partial Granger Causality

Guo (Guo et al., 2008) proposed a new approach, partial Granger causality to eliminate the influences of exogenous inputs and latent variables. Inspired by the definition of partial correlation in statistics, Guo extended the framework of conditional Granger causality by eliminating the influence of latent variables from the predictions of one time series both with and without the second time series. This method is useful to

uncover the underlying causal interactions among multiple time series in the situation with perturbations of exogenous inputs and latent variables.

1.4.5 Multiple Realizations Granger Causality

In neurocognitive applications, it's typical that experiments are conducted with repeated tasks while time series of brain activity are recorded simultaneously. In such block design or multiple trials design, brain causal interactions may change over time. To address such issue of time-varying property, a concept of dividing long time series into short segments, i.e., short windows, is proposed in several researches. Hesse (Hesse, Möller, Arnold, & Schack, 2003) proposed a short window approach to investigate directed causal influences based on electroencephalography (EEG) data. Ding (Ding et al., 2000) incorporated short sliding windows in MVAR model estimation based on event-related potential time series. Each window can be treated as an independent realization of a statistically stationary process and hence can be represented by a single MVAR model. Non-stationaries due to variation of the mean among multiple realizations can be eliminated by removing the ensemble mean, which is defined as the average values of each variable at each time point across trials. The estimation of MVAR model can be implemented by the Levinson, Wiggins, Robinson (LWR) algorithm (Haykin & Kesler, 1983; Morf, Vieira, Lee, & Kailath, 1978), whose procedures are more robust in the context of maximum entropy (Ding et al., 2000; Ding et al., 2006). This approach assumes A constraint of this approach is that each window at least has np observations (Seth, 2010).

1.4.6   Spatial-temporal Granger Causality

Luo et al. (Luo et al., 2013) proposed a spatial-temporal Granger causality approach, which estimate Granger causal interactions with a focus on time-varying properties caused by physiological oscillations. The estimation of such dynamic Granger causal structure was established by dividing time series data into optimal time window, calculating the local Granger causality at each window and then averaging across windows. This estimate was defined as average Granger causality. This measure outperformed the classic Granger causality in terms of increased consistency across consecutive scanning sessions for the same subject. Spatial-temporal Granger causality is valuable with a research interest in dynamic Granger causal interactions.

CHAPTER 2:   RESEARCH OVERVIEW

2.1   <u>Research Gaps</u>

2.1.1   Chronic Sleep Deprivation

Total sleep deprivation is one kind of sleep deprivation and is favored by many researchers on this topic because it offers a low cost but effective means of studying sleep deprivation. However, some studies (Belenky et al., 2003; H. Van Dongen, Rogers, & Dinges, 2003) have shown that cumulative performance changes induced by chronic sleep deprivation might be equivalent to those induced by even the most severe total sleep deprivation. Additionally, chronic sleep deprivation individuals required a longer recovery time. This means chronic sleep deprivation usually has a larger effect, making it a more sensitive method. Remarkably, modern society showed a habitable pattern of chronic sleep deprivation. Thus, it would be piratical to further investigate the effect of chronic sleep deprivation on sustained attention task, not only in the context of neurocognitive task performance, but also in terms of functional mechanisms driven by brain modulation.

2.1.2   Brain Causal Interaction Following Sleep Deprivation

The ability of neurocognitive functions in waking is determined by the interaction of brain areas. Brain activation and functional connectivity studies revealed that sleep deprivation brought either enhanced or inhibited influence on attention control

mechanisms, including goal-oriented modulation, extrinsic stimuli attentional directing, visual sensory processing working memory, and other functional connectivity within systems. However, few studies addressed the issues that how sleep deprivation affects brain effective connectivity, which measures the directed causal influences between brain areas. Additionally, sleep deprivation may provoke competitions between endogenous and exogenous attentional modulation mechanism. A summary of mechanisms involved in such attention control was shown in Figure 3. However, few studies demonstrated the effect of sleep deprivation on the effective connectivity which served in goal-oriented attention control and stimuli-driven modulation. Estimation of effective connectivity is sensitive to predefined brain structural model. An inadequate structural model selection may lead to spurious conclusions of brain casual interactions (Roebroeck, Formisano, & Goebel, 2011). Consider the lack of studies about brain causal interaction following sleep deprivation, an exploratory research is needed to detect brain structural model involved in sustained-attention task and its causal interactions following sleep deprivation.

2.1.3 Time-varying Property of Brain Causal Structure

Brain activity possessed time-varying properties, which should be measured in brain causal structure. In addition, neurocognitive experiments are commonly conducted in repeated realizations, which may contribute to inter-realization variation. Recently, some methods and mathematical frameworks have been proposed to address this issue of dynamic causal structure (Ding et al., 2006; Hesse et al., 2003; Luo et al., 2013). It would

be valuable to study at the changes of brain causal interactions with respect to time, following sleep deprivation.

2.1.4 Relating Brain Activity to Neurocognitive Performance

Some researchers have linked brain activity to task performance via correlation methods (Mo, Schroeder, & Ding, 2011; Wen, Yao, Liu, & Ding, 2012; Zhang, Wang, Bressler, Chen, & Ding, 2008). Some researchers developed mathematical regression model to predict task performance based on brain regional activation following sleep deprivation (Chee & Tan, 2010; Chee et al., 2008). However, few studies focused on linking the brain effective connectivity to task performance, let alone the effect of sleep deprivation on such association. Studies are needed to relate changes of brain causal interactions to changes of neurocognitive performance following sleep deprivation.
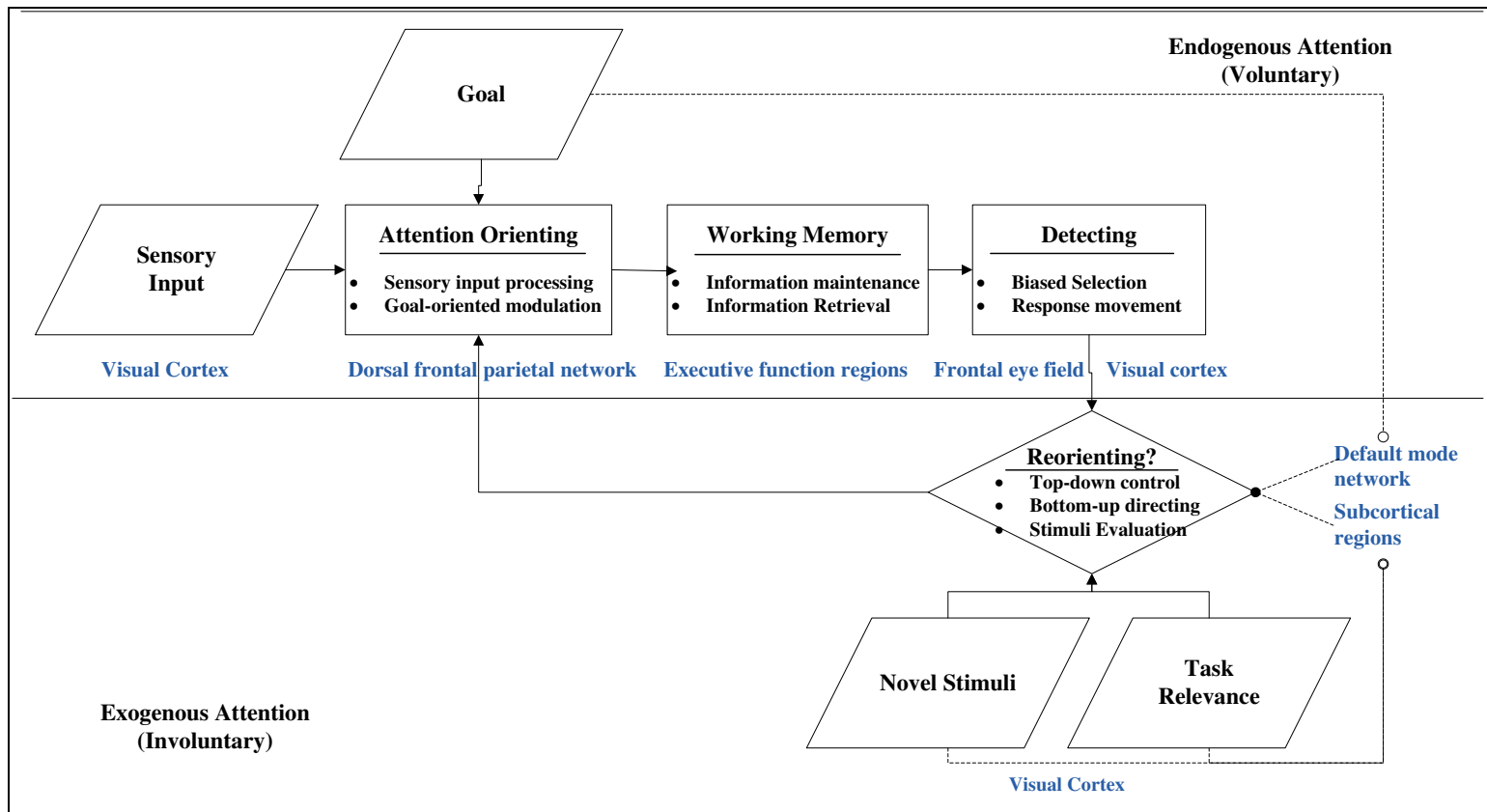
Figure 3 Detailed Attention Control Cognitive Model

2.2   Problem Statement

The focus of this study was to investigate the effect of sleep deprivation on the relationship between brain effective connectivity and changes of performance in a visual spatial sustained-attention task. Since this research was exploratory, there was no hypothesis predefined before analysis. Instead, three main research problems were assessed, including:

- Does sleep deprivation influence task performance?

- Does sleep deprivation influence the model of brain effective connectivity?

- How does changes in brain effective connectivity relate to changes of task performance induced by sleep deprivation?

The first problem was to assess the effect of sleep deprivation on performance measures, including accuracy and response time, in a visual spatial sustained-attention task. Accuracy measured the proportion of correct responses of all trials in each session. Response time measured the average amount of milliseconds until participants gazed at the target stimuli in each session. If significance changes of performance measures were found between the SD condition and the RW condition, the next problem would arise about the underlying neurocognitive mechanism that caused such changes of task performance. Neurocognitive mechanism would be analyzed by developing a model of brain effective connectivity in each condition, which also served as a basis of comparison. If brain effective connectivity differed between the RW condition and the SD condition, there would be a need to address the third problem that how changes of task performance was driven by changes in brain effective connectivity.

2.3   Research Methodology Outline

This research was conducted in a three-phase methodology, shown in Figure 4, to address each of all three research problems. Table 4 demonstrated the list of methods applied in each phase to address the subquestions of each main research problem.

In phase I, whether sleep deprivation had a significant effect on task performance was tested via the analysis of variance (ANOVA), followed by a paired t-test to investigate the change of task performance induced by sleep deprivation. Task performance measures included accuracy and response time. In phase II, a short window Granger Causality approach was applied to develop the model of brain effective connectivity in the RW condition and in the SD condition, respectively. One session in an experiment was treated as one short window. For fMRI data in each session, Granger causality (Granger, 1969) was applied to calculate lobe-wise causal influences among 10 brain areas. Causal influence results were averaged across sessions to create one matrix for each participant. This matrix was averaged within each condition to formulate a model of brain effective connectivity, which also served as a basis of comparison. In phase III, the change of brain effective connectivity after sleep deprivation was linked to the change of response time via Spearman rank correlation analysis.
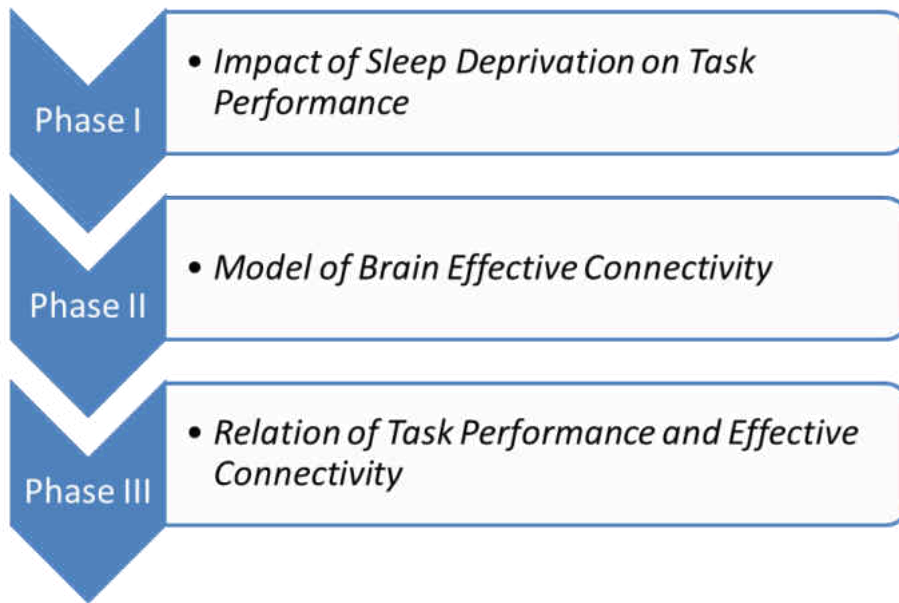
Figure 4 Three-phase Research Methodology

Table 4 Research Methodology Overview

Phase	Research Problems	Research Subquestions	Methods
Phase I	Impact of Sleep Deprivation on Task Performance	i. Does sleep deprivation impact on task performance? ii. What's the change of task performance after sleep deprivation?	The analysis of variance (ANOVA) Paired t-test
Phase II	Model of Brain Effective Connectivity	i. What's the brain structural model involved in visual spatial task? ii. What's the model of brain effective connectivity in the SD condition and in the RW condition, respectively? iii. What's the change of brain effective connectivity after sleep deprivation?	Short window Granger Causality Approach
Phase III	Relation of Task Performance and Effective Connectivity	i. How does changes in brain effective connectivity relate to changes of task performance induced by sleep deprivation?	Spearman Rank Correlation

CHAPTER 3:   RESEARCH DATA

3.1   Experiments

Experiments, analyzed in this research, were conducted by Dr. Fafrowicz and her colleagues at Neuroergonomics Department at Jagiellonian University, Krakow, Poland (Fafrowicz, Marek, Oginska, Beldzik, & Domagalik, 2012). Experiments included the collection of all fMRI data, and all eye tracking data.

3.2   Subjects

Dr. Fafrowicz included thirteen healthy young women (age 23.4 ± 2.0 years) participated in this study. All of them were right-handed, right-eyed dominant, normal or corrected-to-normal vision, nonsmoker and drug-free. None of them showed elevated level of daytime sleepiness, as controlled with Epworth Sleepiness Scale (Johns, 1991) nor sleep problems. Participants were informed about the procedure and goals of the study and gave their written consent. Participants were then trained by Dr. Fafrowicz and her colleagues to ensure familiarity with MR scanner and with the experimental task. The study was approved by the Bioethics Commission at the Jagiellonian University, Krakow, Poland.

3.3   Experimental Procedure

A laboratory experiment was conducted under two conditions: (1) the rest-wakeful (RW) condition, where participants had their usual sleep and (2) the sleep-deprived (SD) condition,

where participants had 3 hours less sleep than their usual sleep, for 7 nights (amounting to 21 h of sleep debt). Three participants were excluded from the final analyses due extensively noise found in functional magnetic resonance imaging brain scans (up to 50% of whole brain scans).

The study was conducted in a laboratory environment at Poland that provided dim light, low noise level, and controlled room temperature. Participants visited the laboratory three times. The first session consisted of a briefing on the experimental procedure, and those that volunteered undertook some practice on the attention task. The second and third visits involved participating in the EOG experiment. The first experimental session took place 1 day after the initial visit. The order of the two experimental sessions (RW, SD) was counterbalanced across all participants. The sessions were separated by at least 2 weeks to minimize the residual effects of sleep deficit on performance of a sustained-attention task. During experimental days, participants were allowed to engage in nonstrenuous activities (e.g., reading, conversing, and watching videos). Research assistants observed the participants and were instructed to prevent them from napping by verbal reminders. Subjects were not allowed to drink or eat substances containing alcohol or caffeine (e.g., tea, chocolate) either during the day of the experiment or during the previous 48 h. Before attempting each of the performance tasks, participants completed the Activation-Deactivation Adjective Check List (Thayer, 1989) to reflect their energy, tiredness, tension, and calmness. Participants also recorded their sleepiness using the Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990).

3.4 Eye Tracking

Dr. Fafrowicz applied a Saccadometer Research MRI system (Ober-Consulting, Poland) to monitor eye-position. The system measures right eye movement in horizontal axis using direct near-infrared technology. It has 500 Hz sampling frequency, measuring range ±20° of visual angle and average spatial resolution of 15'. Eye-tracking data were analyzed using ResearchAnalyzer software (Ober-Consulting, Poland). Saccades were detected with the use of a velocity criterion - eye movements faster that 5 deg/s. Eye reaction time was calculated as difference between stimulus appearance and the beginning of saccade.

3.5 Tasks

Dr. Fafrowicz developed sustained-attention tasks used in this research based on spatial cuing paradigm (Fafrowicz et al., 2010; Posner, 1980; H. P. A. Van Dongen et al., 2003), shown in Figure 6. In our study, central cue (engaging covert orienting attention) was presented to voluntarily direct spatial attention and eye movement to the target location (employing overt orienting attention) (Fafrowicz et al., 2010).

Before the experiment began, the subject was asked to attach eye movement registration equipment, which was integrated with a stimuli generation panel, to her head. The panel was located approximately 3 cm from the subjects' eyes, shown in Figure 1. Each experimental trial started with a fixation point presented in green laser diode in the center of the panel screen. Simultaneously, a cue was presented as a red laser diode at 1^0 to the right or left of the fixation point for 300 ms. After 300 ms to 800 ms, a target stimulus would flash for 500 ms at 10^0 to the

right or left of the fixation point, which was followed by an inter-trial interval of 1300 ms to 4300 ms. Then a new trial would start immediately. Each subject was instructed to direct her gaze and attention straight ahead towards the fixation point at the beginning of each trial and then execute a saccadic eye movement to shift her gaze and attention to the target as soon as possible only if they were preceded by cue. Both speed (reaction time latency) and accuracy of saccadic movements were registered.

There were two types of cue: valid cue and invalid cue. Valid cue indicated target stimuli would appear at the same side as the cue, while invalid cue referred that target stimuli would appear at the opposite side as the cue. Also, there was a control group, no cue. Subjects should inhibit eye movement to the target stimuli if no cue was presented earlier.

The subjects performed the sustained-attention tasks, starting at 22:00 h. In each 42-minute sessions, 598 trials with 58% of congruent cues, 15% of incongruent cues and 27% of no cues were presented. The presentation of more congruent cues was designed to encourage observers to attend to the cued location(H. P. A. Van Dongen et al., 2003).

3.6   fMRI Data Acquisition

Magnetic resonance imaging (MRI) was recorded by colleagues at Poland using a 1,5T Signa HDxt General Electric (GE Medical Systems, Milwaukee, WI). High-resolution, whole-brain anatomical images were acquired using T1-weighted sequence. A total of 60 axial slices were obtained (voxel dimension = $0.4 \times 0.4 \times 3$ mm^3; matrix size = 512×512, TR = 25.0 s, TE = 6.0 ms, FOV = 22×22 cm^2, flip angle = 45°) for coregistration with the fMRI data. Functional

T2∗-weighted images were acquired using an echo planar pulse sequence with a TR of 3 s, TE of 60 ms, matrix size of 128 × 128, FOV of 22 × 22 cm2, spatial resolution of 1.9 × 1.9 × 6 mm3, and flip angle of 90°. Whole brain image was covered with 20 axial slices, taken at an interleaved fashion. The first three images of each session were excluded from functional analysis to allow for T1 equilibrium effects. One functional session lasted 42 min and 15 sec.

Figure 5. Eye Tracking System in the Study (Fafrowicz et al., 2010)
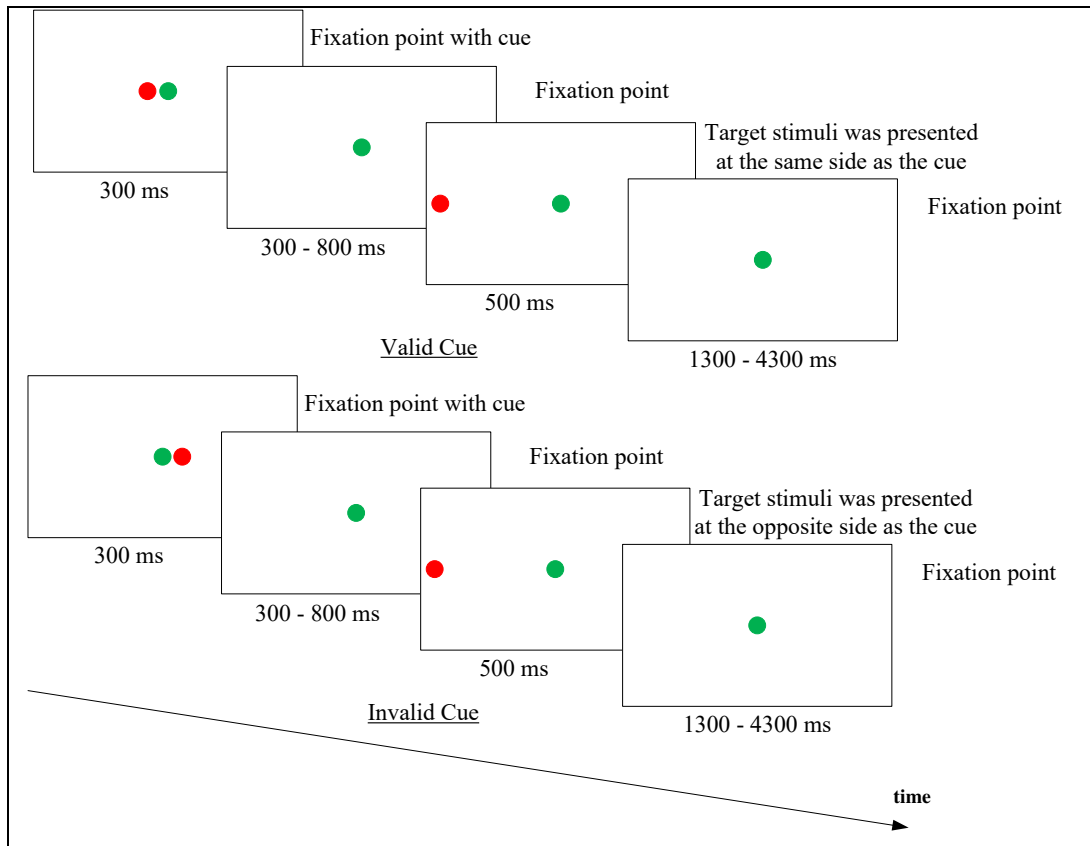
Figure 6 Experimental Task

3.7   **fMRI Data Preprocessing**

Dr. Fafrowicz and her colleagues applied standard preprocessing procedure with Analysis of Functional NeuroImage software (Cox, 1996). First, each 3D image was time-shifted so that the slices were aligned temporally. After head motion correction, the functional EPI data sets were zero-padded to match the spatial extent of the anatomic scans, and then coregistered. Anatomical and functional images were transformed into a coordinate system of Talairach (Talairach & Tournoux, 1988). The functional data were then smoothed using a full-width at half maximum isotropic Gaussian kernel of 8 mm. During scaling procedure, voxels with low-signal

intensity located outside the brain were excluded from functional images by a clipping function. Preprocessed fMRI Data were used in the research as subject's brain scans in the visual spatial sustained-attention task.

Ultimately, each subject had about 70 brain scans at each of 806 time points. Figure 7 demonstrated 49 brain scans of subject 5 at the 100th time point. An example of one brain slice was presented in Figure 8. One brain scan is a 128 * 128 matrix. Each voxel in a brain scan represented a three-dimensional ($0.4*0.4*3$ mm^3) rectangular cuboid of brain anatomical structure. One voxel could contain millions of neurons and synapses (Huettel, Song, & McCarthy, 2004), whose level of BOLD response was represented with a particular color based on the color scale. Red referred to higher activation level, while blue referred to lower activation level.
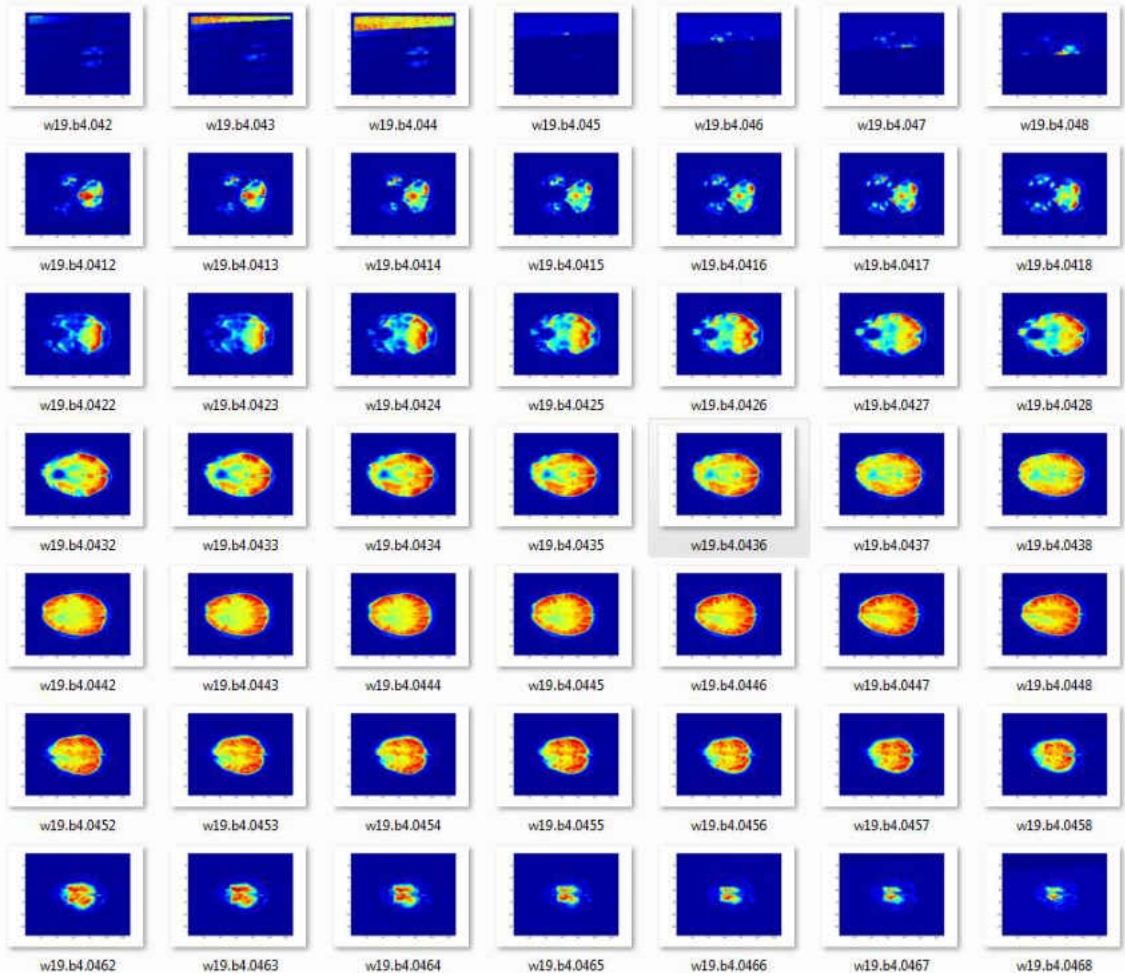
Figure 7 An Example of Brain Scans of Subject 5 at one time point (49 Slices)
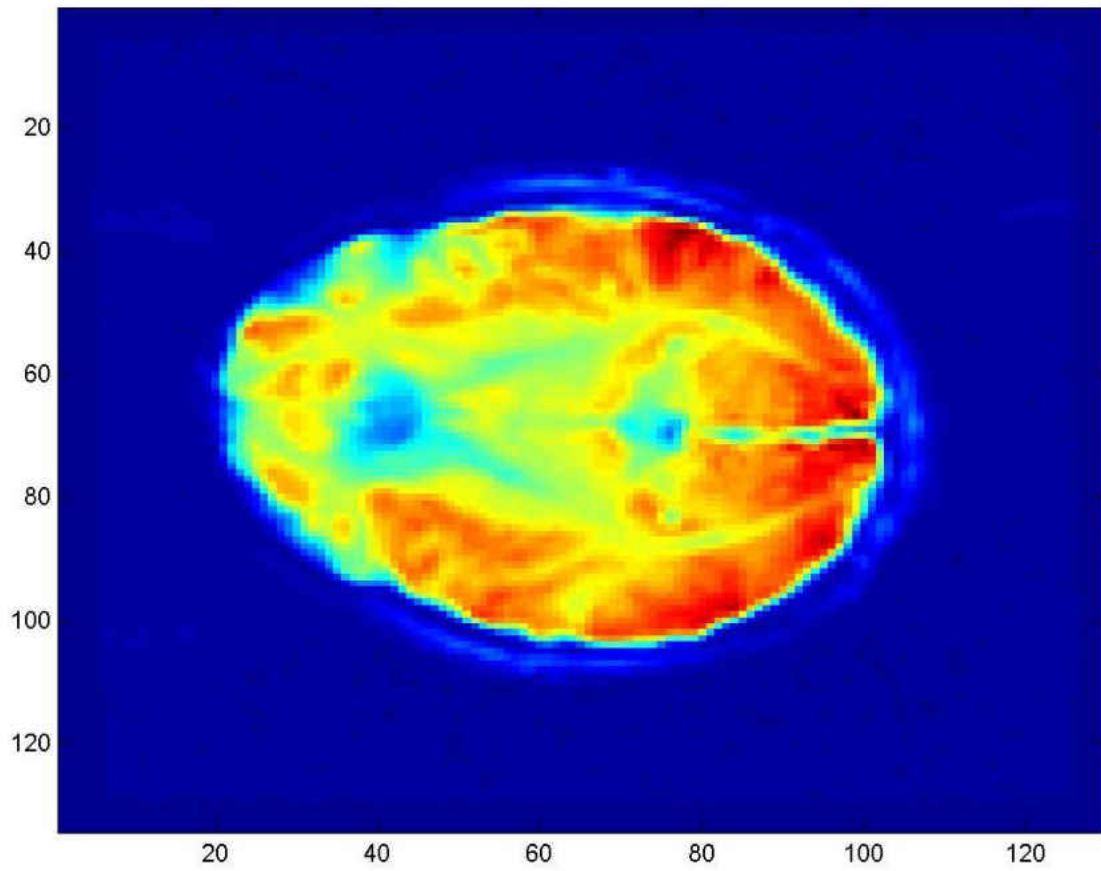
Figure 8 An Example of One Brain Scan of Subject 5 at one time point

CHAPTER 4:   PHASE I TASK PERFORMANCE

This section demonstrated the expected outputs of behavioral analysis and the interpretation about how sleep deprivation impacts on task performance.

4.1   Methods

Two performance measurements were utilized: accuracy and response time. These two performance measures were used in each window for each subject. One window represented an experimental session. For a given window, accuracy measured the proportion of the number of correct responses by the number of total trials. Response time measured the average response latency in correct responses within one window. Two factors repeated ANOVA analysis was applied to investigate the impact of condition and session on both accuracy and response time in visual sustained-attention task. In addition, paired t test was conducted to calculate the 95% confidence interval for the difference of mean performance measures between in rest-wakeful condition and in sleep-deprived condition.

4.2   Results

Ten subjects participated in the visual sustained-attention task. ANOVA analysis of accuracy, shown in Table 5, showed significant inter-individual difference (F = 201.84, p = 0.000) and significant across-session difference (F = 2.17, p = 0.014). ANOVA analysis of

response time demonstrated significant inter-individual difference (F = 123.93, p = 0.000) and significant difference between in the RW condition and in the SD condition (F = 2.17, p = 0.014).

Table 5 ANOVA Analysis of the Impact of Condition and Session on Accuracy

Accuracy	Degrees of Freedom	Sum of Squares	Mean Squares	F statistics	P value
Subject	9	84310.8	9367.9	201.84	0.000
Session	12	1207.0	100.6	2.17	0.014
Condition	1	91.8	91.8	1.98	0.161

Table 6 ANOVA Analysis of the Impact of Condition and Session on Response Time

Response Time	Degrees of Freedom	Sum of Squares	Mean Squares	F statistics	P value
Subject	9	175597	19510.7	123.93	0.000
Session	12	2327	193.9	1.23	0.263
Condition	1	657	657.2	4.17	0.042

Since sleep deprivation only had significant effects on response time, it was used as the performance measure. A paired t-test with a 95% confidence interval was conducted on responses time and condition, shown in Table 7. The difference of response time between in the RW condition and in the SD condition is (0.22, 7.22). Since this confidence interval doesn't contain a zero, null hypothesis about no difference between two population means is rejected. A positive interval means that response time in RW is longer than the one in the SD condition. In other words, subjects responded faster while sleep deprived.

Table 7 Pair-T test on Response Time

	Sample Size	Rest-wakeful	Sleep-deprived	T statistics	P value
Response Time	120	153.51 ± 28.90	149.79 ± 30.83	2.10	0.038

95% CI for mean difference: (0.22, 7.22)

CHAPTER 5:   PHASE II BRAIN EFFECTIVE CONNECTIVITY

This section summarized the expected outputs of brain effective connectivity. The primary question addressed in this section focused on how brain works to perform sustained-attention task in sleep-deprived condition and in rest-wakeful condition. Specifically, investigation was conducted to find out how brain areas connect with each other in each condition and the difference of functional integration pattern between in rest-wakeful condition and in sleep-deprived condition.

5.1   Methods

A three-step approach was taken to answer the research question about how the brain functions in the sustained-attention task: 1) Select region-of-interests (ROIs); 2) Analyze effective connectivity between ROIs; 3) Calculate residual network of effective connectivity between sleep-deprived and rest-wakeful condition.

5.1.1   ROI Selection

Brain regions were identified based on automated anatomical labeling (Tzourio-Mazoyer et al., 2002), a hierarchy brain segregation system. This system described three levels of brain regions, from bottom to middle and then to top level brain structural model.

The bottom level labels refer to 116 brain regions. The middle level labels refer to 14 brain surface-level areas. The top level labels refer to 9 brain lobe-level areas. The list of

anatomical regions of interest defined in each hemisphere and their label can be found in Dr. Tzourio-Mazoyer's research (Tzourio-Mazoyer et al., 2002).

I labeled each voxel of all brain scans into one of the 9 AAL surface-level brain areas using NFRI_functions toolbox (Singh, Okamoto, Dan, Jurcak, & Dan, 2005). The time course of BOLD responses in a given ROI was calculated by dividing the summation of all voxels' BOLD time series in that area by its volume.

5.1.2   Analyze Effective Connectivity between ROIs

To run this analysis, the characteristics of Granger causality mapping (Roebroeck et al., 2005), short window Granger causality analysis (Ding et al., 2006), and spatio-temporal Granger causality (Luo et al., 2013) were combined. A short-window Granger causality approach was developed to map the pairwise effective connectivity across the entire brain and provide an average Granger causality as the measurement of the influence exerted from one brain area to another. This approach was an exploratory method to identify the directed influence over the entire brain and to select task-related brain functional structure (a task-related effective connectivity network). Therefore, all 10 ROIs were included in this analysis.

This approach included six steps, shown in Figure 9. First, the entire time course of BOLD response of each ROI was split into 13 windows. Each window represented the BOLD time series in one of the 13 sessions through the entire experiment, which has been an effective way to present the time-varying causal relations among brain areas (Ding et al., 2000; Hesse et al., 2003; Seth, 2010). Second, ensemble mean, the average task-level response, were estimated by averaging BOLD responses for each variable at each time point across windows. This

ensemble mean was removed from the BOLD responses in each window to yield the residual

fluctuations, which represented realizations of the underlying stochastic process (Ding et al.,

2000; Seth, 2010; Wen et al., 2012). Third, temporal mean also was removed from BOLD signal

within each window to meet the zero-mean assumption by the vector autoregressive (VAR)

model (Ding et al., 2000; Ding et al., 2006).   Fourth, window Granger causality for a given pair

of ROIs was calculated within each window. One pair of Granger causality represents the

Granger influence exerted from one brain area to another. Ordinary-least-squares method was

applied to compute the first-order vector autoregressive (VAR) model (Seth, 2010). Significant

window Granger causality was then determined by F-test (Greene, 2003). Fifth, for a given

subject, subject-level Granger causality matrix was calculated by averaging significant window

Granger causality for each pair of ROIs across 13 windows. Significance test of this average

Granger causality was conducted via surrogate methods, due to the lack of known statistical

distributions (Seth, 2010).

A set of 1000 simulations were conducted based on surrogate time series BOLD signals

respectively in the context of bootstrapping and random permutation. Both bootstrapping

distribution and permutation distribution were established via the kernel method. Significance

level of test average Granger causality was generated by examining bootstrapping distribution,

while significance threshold was generated by examining permutation distribution. In addition,

false discovery rate (FDR) correction was applied for multiple comparisons (Roebroeck et al.,

2005; Wen et al., 2012). Average Granger causalities whose significance level exceeded

significance threshold were selected to formulate subject-level significant Granger causality

matrix, which represents the subject's effective connectivity network. Sixth, population-level

effective connectivity network was identified by averaging subject-level significant Granger causality matrix across 10 subjects. The strongest 20 Granger causalities were selected to generate population-level effective connectivity network.
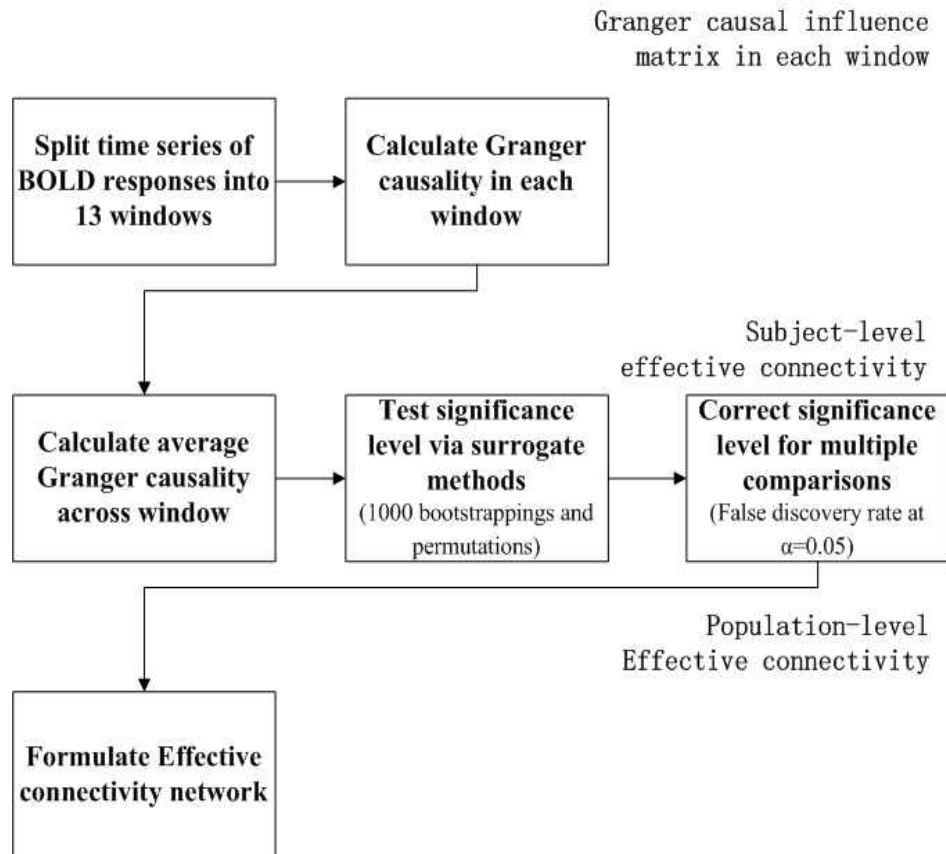
Figure 9 Steps of the Short Window Granger Causality Approach

Such an exploratory approach would allow: 1) The investigation of task-related brain structural model and interactions between segregated areas based on information from the data (Roebroeck et al., 2011); 2) The investigation of the dynamic causality structure in Granger causality analysis and provided larger measures of Granger influence exerted from brain area to another (Luo et al., 2013).

5.1.3   Residual Network of Effective Connectivity

The residual network of Granger causal influences was calculated to quantitatively analyze the difference of effective connectivity between in the RW condition and the SD condition. Three steps were conducted to calculate the residual network of Granger causal influences. First, for a given pair of brain areas, the difference of Granger causal influence between the RW condition and the SD condition were calculated for each subject. Second, the differences of Granger causal influence for each pair of brain areas across subjects were averaged. Third, the strongest 20 residual Granger causal influences were selected to formulate Granger causal influence residual network.

5.2   **Results**

5.2.1   ROI Selection

In both the RW and SD conditions, a maximum of twelve brain surface-level areas were identified based on automated anatomical labeling (AAL) among 10 subjects: 1. Central regions, 2. Lateral frontal lobe, 3. Medial frontal lobe, 4. Orbital frontal lobe, 5. Lateral temporal lobe, 6. Lateral parietal lobe, 7. Medial parietal lobe, 8. Lateral occipital lobe, 9. Medial and inferior occipital lobe, 10. Limbic lobe, 11. Sub cortical gray nuclei, 12. Cerebellum. The 4th region, Orbital frontal lobe, was only identified in 60% of subjects in RW condition and in 70% of subjects in SD condition. In addition, the 10th region, Limbic lobe, was only labeled in 60% of subjects in RW condition and in 70% of subjects in SD condition. Considering the goal of this

research is to find a general brain functional pattern related to visual sustained-attention task, I

eliminated the 4th and 10th regions from ROIs.

At last, ten ROIs were included in the following brain functional activity analysis: 1.

Central regions (CR), 2. Lateral frontal lobe (LF), 3. Medial frontal lobe (MF), 5. Lateral

temporal lobe (LT), 6. Lateral parietal lobe (LP), 7. Medial parietal lobe (MP), 8. Lateral

occipital lobe (LO), 9. Medial and inferior occipital lobe (MIO), 11. Sub cortical gray nuclei

(SC), 12. Cerebellum (CB). The list of ROIs was shown in Table 8, in the context of region

number, region labels, and their acronyms. The neuroanatomical structure of ROIs was shown in

Figure 10. Brain areas were labeled with their initials and highlighted in different colors.

Table 8 Region-of-Interests: Number, Labels, and Acronyms

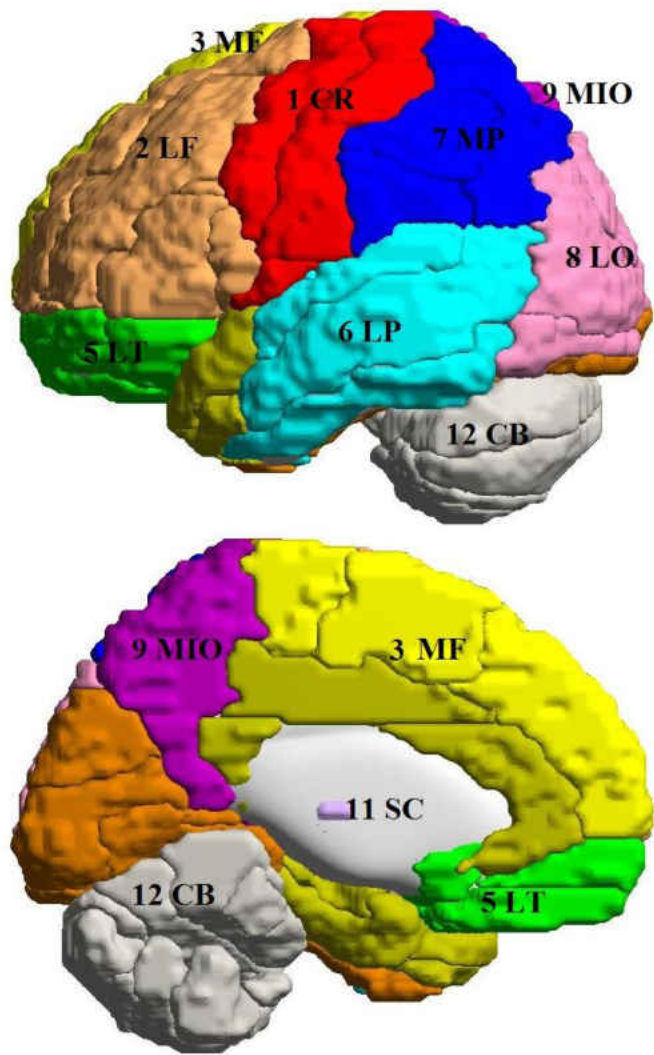| Region Number	Region Labels	Acronyms of Region Labels
1	Central regions	CR
2	Lateral frontal lobe	LF
3	Medial frontal lobe	MF
4	Lateral temporal lobe	LT
5	Lateral parietal lobe	LP
6	Medial parietal lobe	MP
7	Lateral occipital lobe	LO
8	Medial and inferior occipital lobe	MIO
9	Sub cortical gray nuclei	SC
10	Cerebellum	CB

Figure 10 Brain region of Interests (ROIs) in this research

5.2.2   Subject-level Granger Causality

Granger causality was first calculated in each scanning window, i.e., one experimental session, in the RW condition and in the SD condition, respectively. This step was defined as short-window Granger causality, which yielded 13 Granger causal matrices for each participant. Took subject 3 as an example. Significant Granger causality over the entire brain was detected through short-window Granger causality approach. Granger causality matrix from 1st window to 8th window was presented in Figure 12 and those in the rest windows were shown in Figure 13. For subject 3, a dynamic changing Granger causal pattern was observed through all windows. The time-varying properties of causal interaction were confirmed with similar observation from other subjects. The rest results of subject-level Granger causality, involving all other 9 subjects, were shown in Appendix A.

Significance test of a short-window Granger causal matrix was carried out via F-test ($\alpha = 0.05$). Took subject 3 under the RW condition as an example. Figure 11 showed the significant Granger causality matrix within the 2nd window. Each square represents a Granger causality, which passed F-test at $\alpha = 0.05$, exerted from the row brain area to the column brain area. Its strength was shown with the particular color based on color bar shown on the right of the matrix. For example, the square on the second row and the third column referred to the Granger influence exerted from brain area 2 (2nd row), lateral frontal lobe, to brain area 3 (3rd column), medial frontal lobe, with a strength between 0.4 and 0.45.

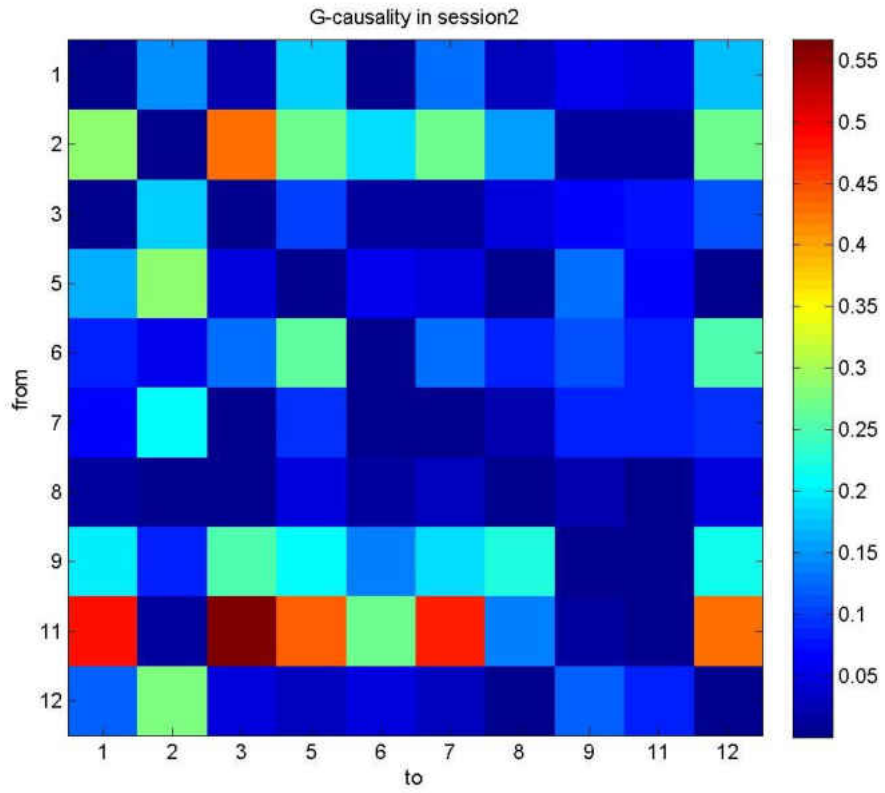Figure 11 Subject 3: Granger Causality Matrix from the Row Region to the Column Region
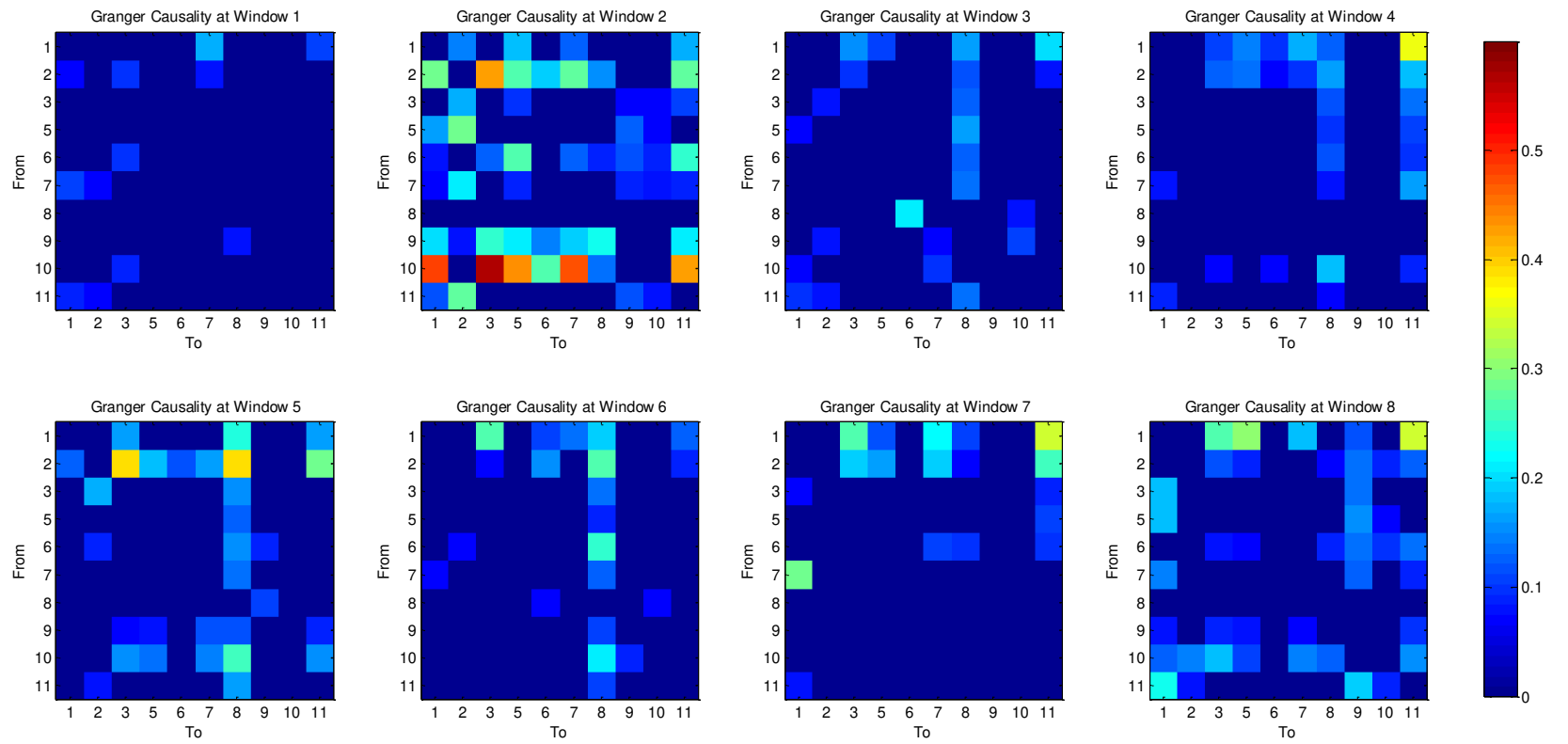(Within the 2nd Window)

Figure 12 Subject 3: Granger Causality Matrix from 1st Window to 8th Window
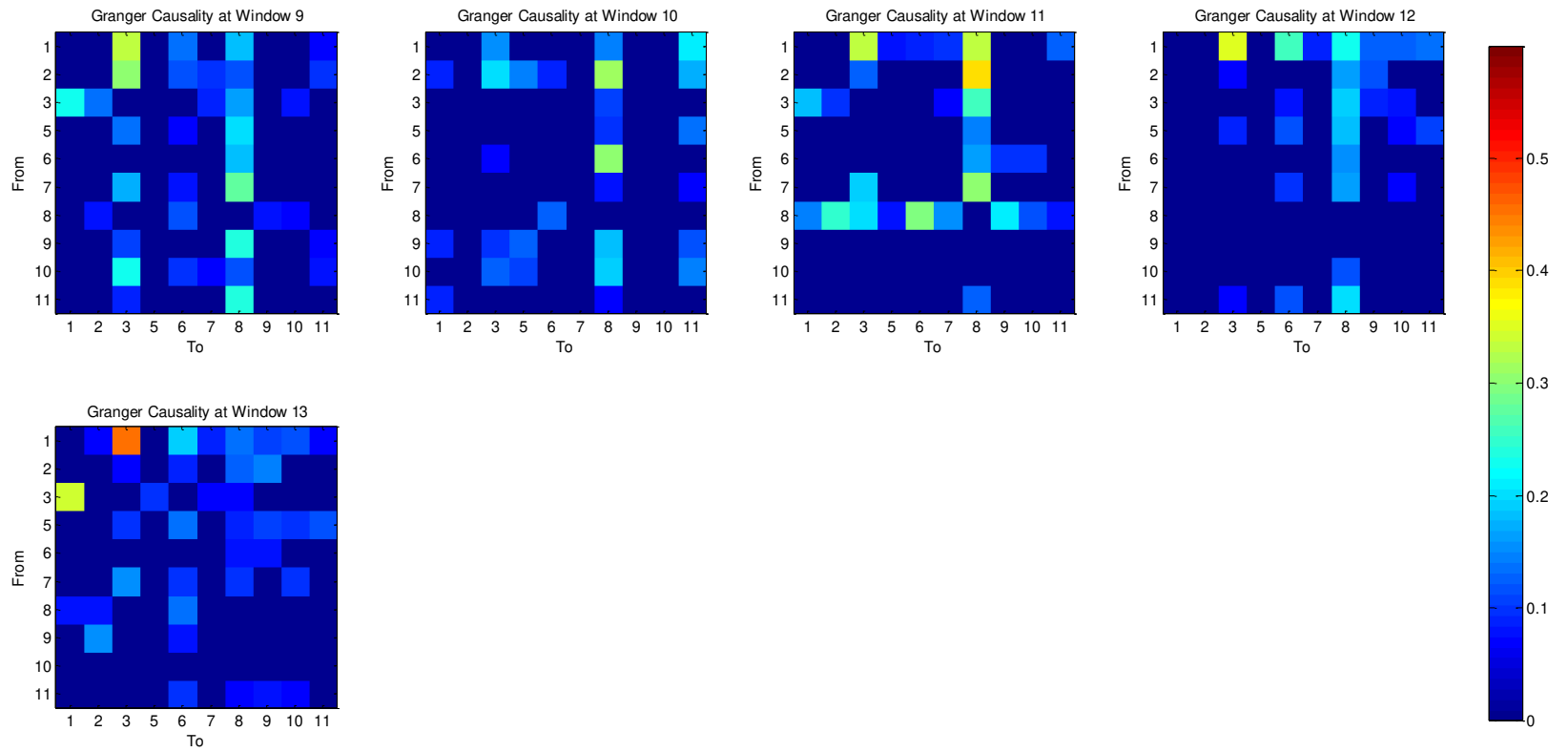(Causal Influence Exerted from the Row Region to the Column Regions)

Figure 13 Subject 3: Granger Causality Matrix from 9th Window to 13th Window
(Causal Influence Exerted from the Row Region to the Column Regions)

For a given subject in one condition, after Granger causality was calculated within each window, an average Granger causality matrix was calculated. This was done by averaging across windows. The significance of a Granger causality between a given pair of ROIs was tested via the bootstrap and permutation surrogate methods at α = 0.05. False Discovery Rate (FDR) analysis were also conducted to correct multiple comparison at α = 0.05. Table 9 demonstrates subject-level average Granger causality of every pair of ROIs of subject 3 as in rest-wakeful condition, in which row labels refer to bran areas sending Granger influence, while column labels refer to the brain areas receiving Granger influence. The region labels related to region acronym were listed in Table 8. The values highlighted in red refer to the significant subject-level Granger causality which passed both significance test and FDR correction for multiple comparisons. The values highlighted in green refer to the average Granger causality which only passed significance test, but failed in FDR correction (over 95.55% of data passed FDR correction). The current Granger causality methods was not applicable to calculate Granger influence within one brain area, which leaded to missing values on the diagonal of the matrix.

Table 9 Subject 3: Average Granger Causality Exerted from Row Region to Column Region

		To									
		CR	LF	MF	LT	LP	MP	LO	MIO	SC	CB
	CR		0.02	0.22	0.09	0.06	0.14	0.13	0.03	0.01	0.19
	LF	0.05		0.18	0.09	0.06	0.10	0.17	0.02	0.00	0.14
	MF	0.08	0.06		0.02	0.00	0.01	0.10	0.02	0.01	0.02
	LT	0.03	0.03	0.02		0.02	0.00	0.09	0.03	0.01	0.06
From	LP	0.02	0.01	0.03	0.06		0.04	0.13	0.03	0.00	0.07
	MP	0.07	0.03	0.03	0.01	0.01		0.10	0.02	0.01	0.03
	LO	0.01	0.02	0.01	0.01	0.07	0.00		0.03	0.02	0.01
	MIO	0.04	0.02	0.05	0.06	0.02	0.04	0.08		0.02	0.07
	SC	0.05	0.01	0.09	0.06	0.03	0.07	0.10	0.01		0.07
	CB	0.07	0.04	0.00	0.00	0.02	0.00	0.08	0.03	0.01	

The significant average Granger causalities were selected to represent subject 3's

Granger causality matrix as under RW, shown in Figure 14, followed by the subject 3's effective

connectivity network under RW, shown in Figure 15. The interpretation of the subject-level

average Granger causality was very similar to the window Granger causality matrix. Each square

represented the subject-level Granger causality between a pair of ROIs by averaging across

windows. The color demonstrated the strength of this connectivity based on the color scale on

the right. In an effective connectivity network, each node refers to one ROI and each link

represented a directed effective connectivity between a pair of ROIs, which were measured as

the Granger influence from one brain area to another as directed by the arrow. For example, there

was a directed link from the lateral occipital lobe to the medial frontal lobe, indicating that the

lateral occipital lobe exerted a Granger influence one the medial frontal lobe.
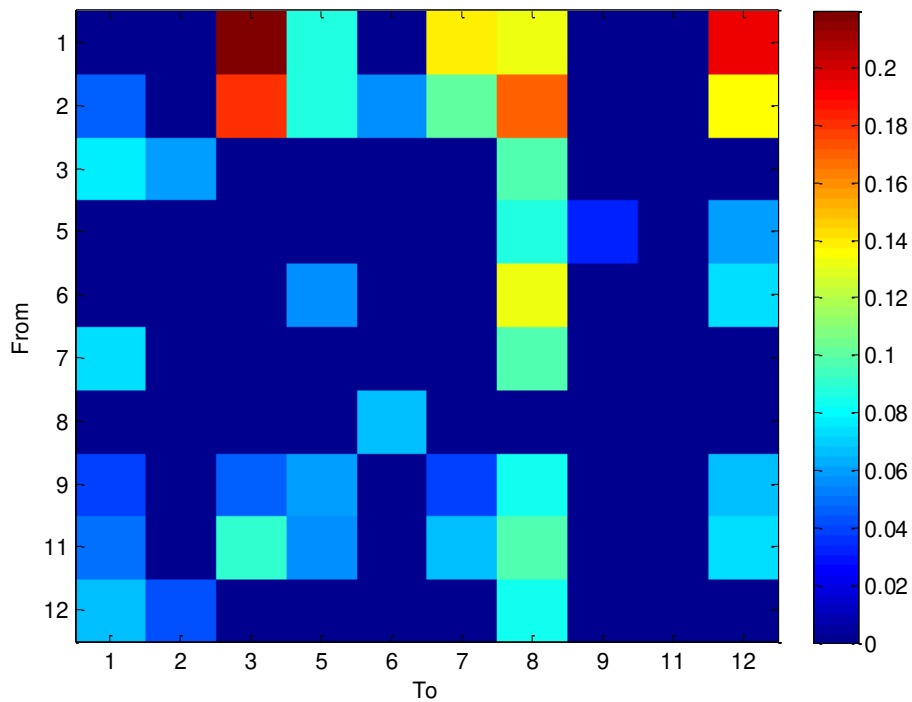
Figure 14 Subject 3: Significant Granger Causality Matrix under RW
(Causal Influences Exerted from the Row regions to the Column Regions)
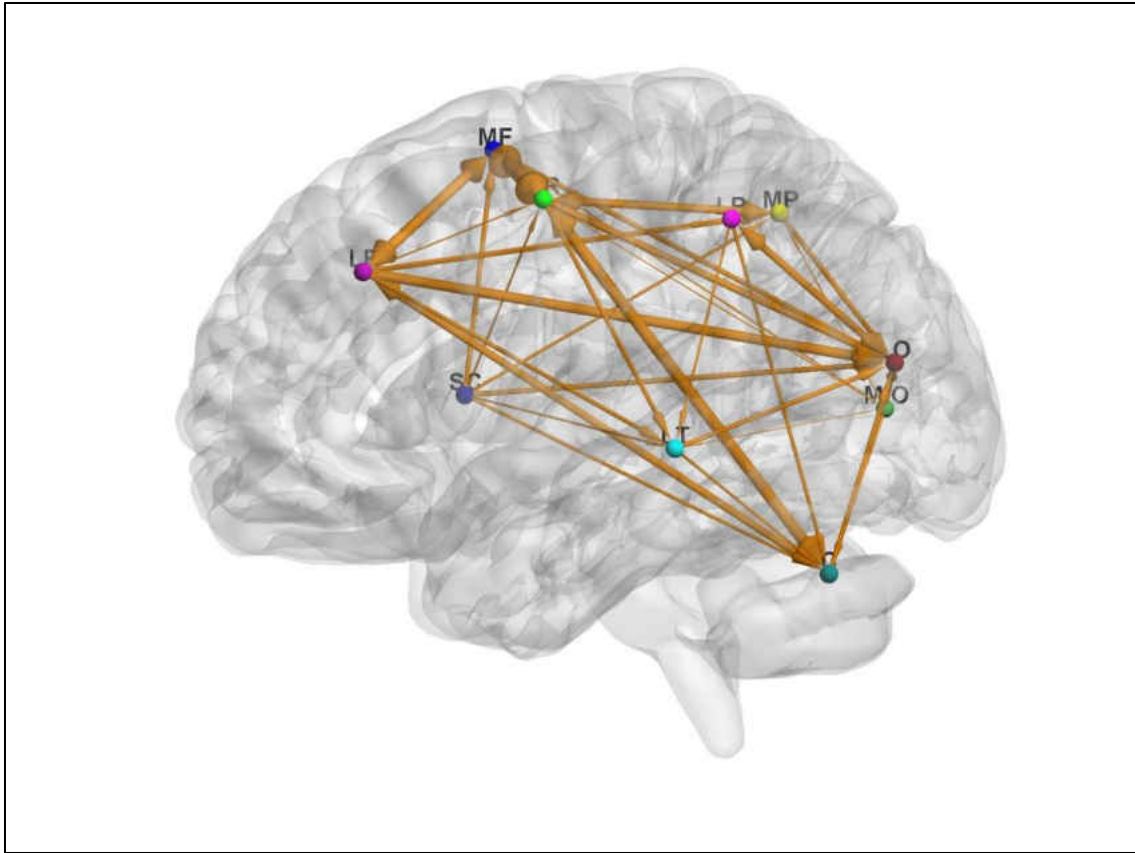
Figure 15 Subject 3: Effective Connectivity Network under RW

5.2.3   Population-level Effective Connectivity Network

For a given condition, a population-level Granger causality matrix was calculated by averaging subject average Granger causalities across subjects under that particular condition. This Granger matrix was used to represent the general effective connectivity under a certain condition. This section demonstrated this effective connectivity in the RW condition and SD condition

5.2.3.1 *Effective Connectivity as in the Rest-wakeful Condition*

In the RW condition, the strongest 20 population –level Granger causalities were selected to formulate the brain effective connectivity network related to the visual sustained-attention task, shown in Figure 16. Each brain area was represented by a node, and each Granger influence exerted from one brain area to another was represented by a link. The direction of the link was shown by the direction of the arrow. Links highlighted in red referred to the bidirectional Granger influences between the pair of brain areas on the two sides of the links. The thickness of the link represented the strength of Granger influence, which measured by population-level Granger causality, shown in Table 10. Seven bidirectional Granger causal influences were found in the RW condition: Central region ↔ Lateral parietal lobe ($F_{CR \to LP} = 0.054$, $F_{LP \to CR} = 0.063$); Central region ↔ Medial frontal lobe ($F_{CR \to MF} = 0.103$, $F_{MF \to CR} = 0.074$); Lateral frontal lobe ↔ Medial frontal lobe ($F_{LF \to MF} = 0.092$, $F_{MF \to LF} = 0.061$); Medial frontal lobe ↔ Lateral parietal lobe ($F_{MF \to LP} = 0.082$, $F_{LP \to MF} = 0.099$), Medial frontal lobe ↔ Subcortical gray nuclei ($F_{MF \to SC} = 0.065$, $F_{SC \to MF} = 0.100$), Lateral parietal lobe ↔ Medial parietal lobe ($F_{LP \to MP} = 0.077$, $F_{MP \to LP} = 0.065$), Medial parietal lobe ↔ Subcortical gray nuclei ($F_{MP \to SC} = 0.057$, $F_{SC \to MP} = 0.070$). Medial frontal lobe also exerted Granger causal influence to the lateral occipital lobe ($F_{MF \to LO} = 0.057$). Lateral temporal lobe received Granger causal influence both from medial frontal lobe ($F_{MF \to LT} = 0.053$) and from lateral parietal lobe ($F_{LP \to LT} = 0.060$). Sub cortical gray nuclei had Granger causal influence on the central region ($F_{SC \to CR} = 0.061$). Cerebellum receives Granger causal influence both from the central region ($F_{CR \to CB} = 0.067$) and from the lateral frontal lobe ($F_{LF \to CB} = 0.057$).
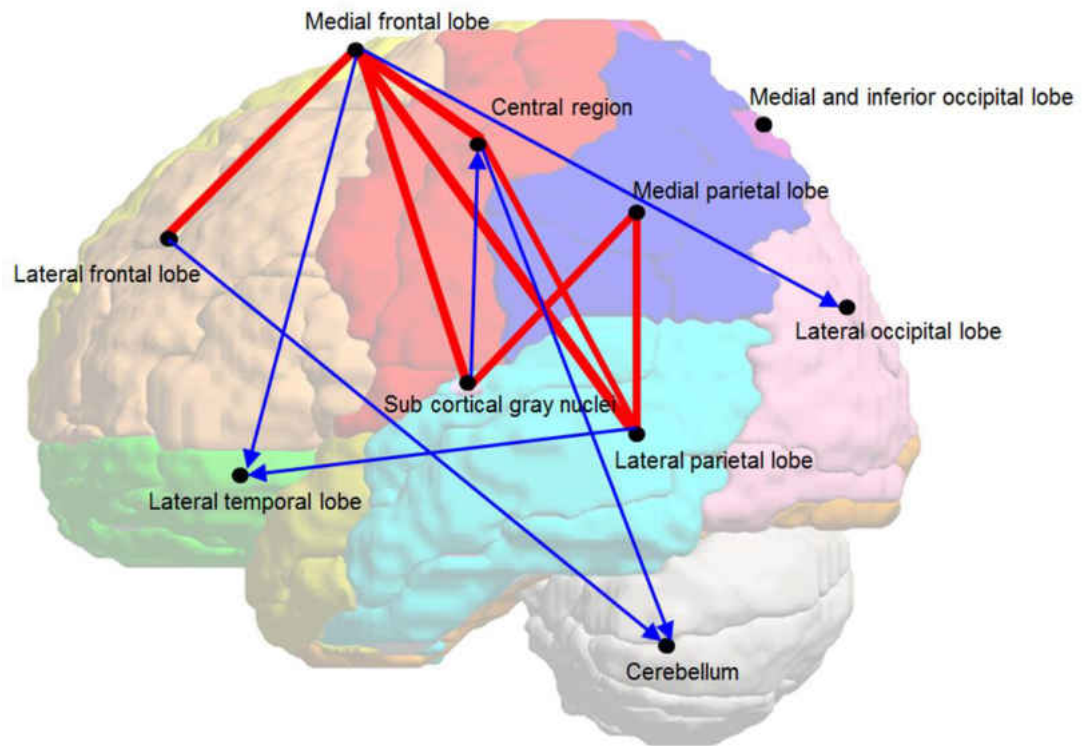
Figure 16 Effective Connectivity as in Rest-wakeful Condition

Table 10 Strongest 20 Population-level Granger Causalities as in Rest-wakeful condition

FROM/TO	CR	LF	MF	LT	LP	MP	LO	MIO	SC	CB
CR			.103		.054					.067
LF			.092							.057
MF	.074	.061		.053	.082		.057		.065	
LT										
LP	.063		.099	.06		.077				
MP					.065				.057	
LO										
MIO										
SC	.061		.1			.07				
CB										

5.2.3.2   Effective Connectivity as in the Sleep-deprived Condition

In the condition, the strongest 20 population –level Granger causalities were selected to formulate the brain effective connectivity network related to the visual sustained-attention task, shown in Figure 17. The way to read the graph was the same as the effective connectivity network as in the RW condition. The strongest 20 Population-level Granger Causalities detected in the SD condition are shown in Table 11. Two bidirectional Granger causal influences were found in the SD condition: medial frontal lobe $\leftrightarrow$ lateral parietal lobe ($F_{MF \rightarrow LP} = 0.107$, $F_{LP \rightarrow MF} = 0.160$), lateral parietal lobe $\leftrightarrow$ medial parietal lobe ($F_{LP \rightarrow MP} = 0.059$, $F_{MP \rightarrow LP} = 0.047$). The central region exerts Granger causal influence to medial frontal lobe ($F_{CR \rightarrow MF} = 0.081$), medial

parietal lobe ($F_{CR \rightarrow MP} = 0.045$) and sub cortical cerebellum ($F_{CR \rightarrow CB} = 0.076$). The lateral frontal

lobe exerted grange causal influence to the cerebellum ($F_{LF \rightarrow CB} = 0.097$) as well as the medial

frontal lobe ($F_{LF \rightarrow MF} = 0.093$). In addition, the medial frontal lobe received Granger causal

influences from the sub cortical gray nuclei ($F_{SC \rightarrow MF} = 0.075$), the lateral occipital lobe ($F_{LO \rightarrow MF}$

$= 0.045$) and medial and inferior occipital lobe ($F_{MIO \rightarrow MF} = 0.075$). The medial and inferior

occipital lobe also brought Granger causal influence on the medial parietal lobe ($F_{MIO \rightarrow MP} = 0.051$)

and the cerebellum ($F_{MIO \rightarrow CB} = 0.068$). The lateral parietal lobe exerted influence to lateral

occipital lobe ($F_{LP \rightarrow LO} = 0.055$) and the cerebellum ($F_{LP \rightarrow CB} = 0.095$). Additionally, the

cerebellum received Granger causal influence from the lateral temporal lobe ($F_{LT \rightarrow CB} = 0.098$),

the lateral occipital ($F_{LO \rightarrow CB} = 0.052$) and the sub cortical gray nuclei ($F_{SC \rightarrow CB} = 0.062$).
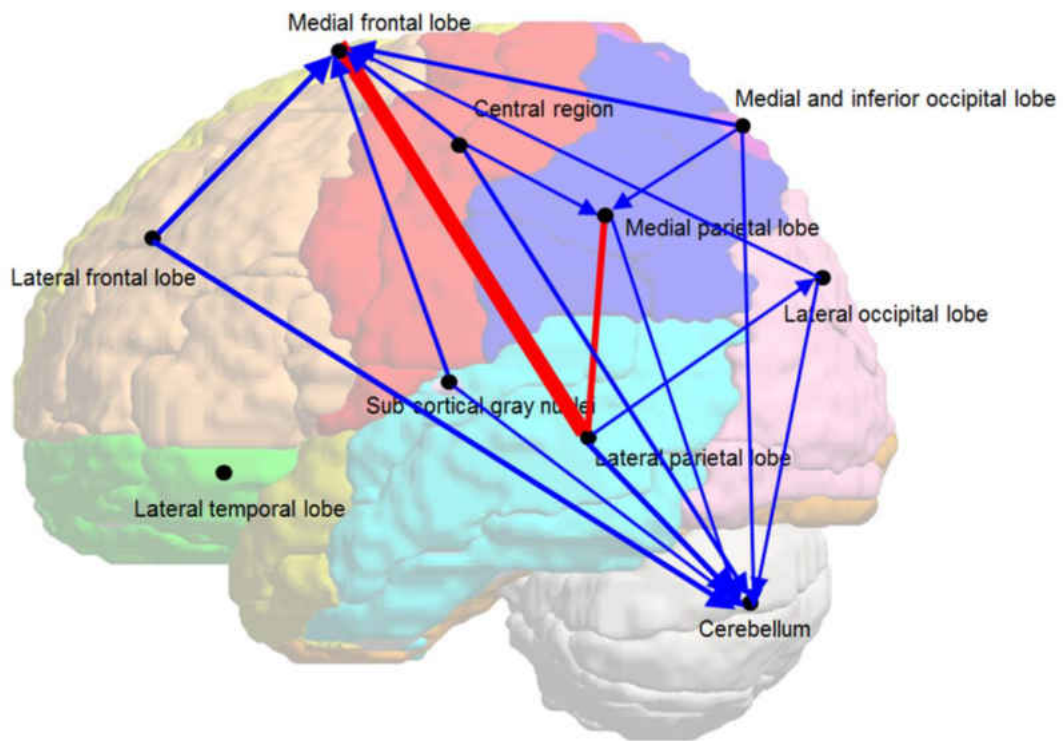

Figure 17 Effective Connectivity as in Sleep-deprived (SD) Condition

Table 11 Strongest 20 Population-level Granger Causalities as in Sleep-Deprived (SD) Condition

FROM/TO	CR	LF	MF	LT	LP	MP	LO	MIO	SC	CB
CR			.081			.045				.076
LF			.093							.097
MF					.107					
LT										.098
LP			.160			.059	.055			.095
MP					.047					.065
LO			.045							.052
MIO			.075			.051				.068
SC			.075							.062
CB										

5.2.4   Residual Network of Effective Connectivity

The difference of Granger causal influences between in the RW condition and in the SD condition was analyzed quantitatively. The strength of residual Granger causality between any pair of ROIs was shown in Table 13. Each row represented the residual Granger causality between one pair of ROIs. Labels on the left demonstrated a single causal interaction structure and values on the right represented the strength of residual Granger causality. The residual network of Granger causal influences was shown in Figure 18, in term of the proportion to the maximum value. Each square represented the residual Granger causal influence from the row area to the column area. Positive sign referred to stronger Granger causal influence in the RW

condition; and vice versa. In addition, color repents the proportion of its strength by the maximum difference of influence.

Take the square on the sixth row and the third column as an example. This square represented the residual Granger causal influence from brain area 6, lateral parietal lobe, to brain area 3, medial frontal lobe, between the RW and the SD conditions. This square referred to a negative value, indicating that Granger causal Influence from lateral parietal lobe to medial frontal lobe is smaller (weaker) in RW condition, but larger (stronger) in the SD condition. In addition, the square was in red, which referred that the residual Granger causal influence from lateral parietal lobe to medial frontal lobe was above 70% of the maximum value of residual Granger causal influences across all 20 pairs of brain areas. The changes of causal influences induced by sleep deprivation were listed in Table 12. Further details were demonstrated as follows.

Granger causal influences, which get stronger after sleep deprivation, include: Lateral frontal lobe → Cerebellum ; Subcortical gray nuclei→Cerebellum; Medial and inferior occipital lobe→Medial frontal lobe; Lateral temporal lobe→Cerebellum; Lateral parietal lobe→Medial frontal lobe; Medial parietal lobe → Cerebellum; Lateral parietal lobe →Cerebellum; Medial and inferior occipital lobe →Cerebellum.

Granger causal influences, which get weaker after SD, include: Central region → Lateral temporal lobe; Central region → Lateral parietal lobe; Central region → Sub cortical gray nuclei; Subcortical gray nuclei →Lateral parietal lobe; Sub cortical gray nuclei →Medial parietal lobe; Medial parietal lobe →Lateral frontal lobe; Medial parietal lobe→Lateral temporal lobe; Medial parietal lobe → Sub cortical gray nuclei; Medial frontal lobe→Lateral occipital lobe; Medial

frontal lobe→Sub cortical gray nuclei; Medial parietal lobe→Sub cortical gray nuclei; Lateral

temporal lobe→Sub cortical gray nuclei.

Table 12 Changes of Causal Influences Induced by Sleep Deprivation (Strongest 20 Values)

Stronger Causal Influences in Sleep Deprivation	Weaker Causal Influences in Sleep Deprivation
Lateral frontal lobe→Cerebellum	Central region → Lateral temporal lobe
Subcortical gray nuclei→Cerebellum	Central region → Lateral parietal lobe
Medial and inferior occipital lobe→Medial frontal lobe	Central region → Sub cortical gray nuclei
Lateral temporal lobe→Cerebellum	Subcortical gray nuclei →Lateral parietal lobe
Lateral parietal lobe→Medial frontal lobe	Sub cortical gray nuclei →Medial parietal lobe
Medial parietal lobe→Cerebellum	Medial parietal lobe →Lateral frontal lobe
Lateral parietal lobe→Cerebellum	Medial parietal lobe→Lateral temporal lobe
Medial and inferior occipital lobe→Cerebellum	Medial parietal lobe → Sub cortical gray nuclei
	Medial frontal lobe→Lateral occipital lobe
	Medial frontal lobe→Sub cortical gray nuclei
	Medial parietal lobe→Sub cortical gray nuclei
	Lateral temporal lobe→Sub cortical gray nuclei

Table 13 Residual Granger Causality (Strongest 20)

| Label of Granger Causal Influence	Difference between in the Rest-wakeful Condition and the Sleep-deprived Condition
Medial and inferior occipital lobe→Medial frontal lobe	-0.031
Medial parietal lobe→Cerebellum	-0.032
Medial and inferior occipital lobe→Cerebellum	-0.039
Lateral frontal lobe→Cerebellum	-0.040
Subcortical gray nuclei→Cerebellum	-0.046
Lateral parietal lobe→Cerebellum	-0.056
Lateral parietal lobe→Medial frontal lobe	-0.061
Lateral temporal lobe→àCerebellum	-0.066
Subcortical gray nuclei→Medial parietal lobe	0.029
Subcortical gray nuclei→ Lateral parietal lobe	0.030
Medial parietal lobe→Lateral temporal lobe	0.031
Medial parietal lobe→Lateral frontal lobe	0.033
Central region →Lateral parietal lobe	0.035
Lateral temporal lobe→Subcortical gray nuclei	0.036
Central region →Lateral temporal lobe	0.037
Medial parietal lobe → Central region	0.04
Central region →Sub cortical gray nuclei	0.042
Medial frontal lobe→Lateral occipital lobe	0.043
Medial parietal lobe→Subcortical gray nuclei	0.049
Medial frontal lobe→Subcortical gray nuclei	0.052
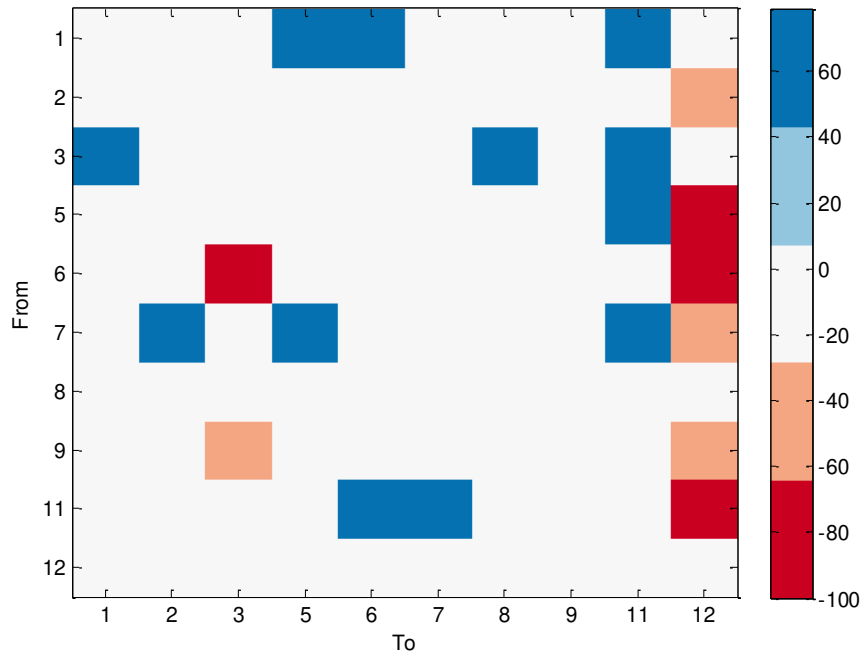
Figure 18 Residual Network of Granger causal influences from the Row Region to the Column Region (Strongest 20 Residual Granger Causal Influences)

5.3 **Discussions**

5.3.1 Brain Region of Interests

Ten brain regions were included in this research. From the view of brain segregation, each region may be specialized for some aspects of perceptual or motor processing functions (Friston, 2011). The list of region-of-interest and their links to particular neurocognitive functions was summarized in Table 14. Further details of region-of-interests were demonstrated in the context of structural model and its link to neurocognive functions based on literature reviews as follows. A quantitative Brain atlas reconciliation analysis was then carried out to

transfer brain regions in other atlas system into AAL atlas system, which then served as a basis of comparison and hence a support to interpret results in this research.

Table 14 Functional Segregation of Ten Region-of-Interests

Neurocognitive Functions	Related Brain Regions
Visualspatial Attention Control	Lateral Frontal Lobe (LF)
	Medial Frontal Lobe (MF)
	Lateral Parietal Lobe (LP)
	Medial Parietal Lobe (MP)
Visual Information Processing	Lateral Occipital Lobe (LO)
	Medial And Inferior Occipital Lobe (MIO)
Global Coordination Across The Whole Brain	Sub Cortical Gray Nuclei (SC)
Working Memory	Lateral Temporal Lobe (LT)
Sensory Processing and Computation	Cerebellum (CB)
Somatosensory and Motor Cortices	Central Region (CR)

5.3.1.1 *Alertness and Attentional Orienting*

Regions engaged in maintaining alertness include thalamic, frontal and parietal regions (Coull, Sahakian, & Hodges, 1996; Marrocco, Witte, & Davidson, 1994), and hippocampal regions (Yoo, Hu, Gujar, Jolesz, & Walker, 2007). Region associated with attentional orienting include superior and inferior parietal lobule, frontal eye fields, and subcortical areas (Corbetta et al., 2000; Posner, 1980; Posner & Cohen, 1984).

Alerting and orienting are two important aspects of attention control neurocognitive function. Intrinsic alertness is defined as wakefulness and arousal, which associated with internal

preparation of stimulus processing (Fan et al., 2009). Orienting involves three operations: disengaging attention from its current focus, moving attention to the new target or modality, and engaging attention at the new target or modality (Posner & Cohen, 1984).

A quantitative comparison between different brain atlas coordinate systems was needed in order to improve interpretation of results by comparing this research with other researches. This procedure was carried out by the online brain atlas reconciliation tool developed by Bohland and his colleagues (Bohland, Bokil, Allen, & Mitra, 2009). Thalamic labeled in Talairach Daemon (TAL) atlas (Lancaster et al., 2000) coordinate system was contained in Sub cortical gray nuclei in AAL atlas coordinate system. In addition, both lateral frontal lobe and medial frontal lobe in TAL contained some part of frontal eye fields in AAL.

5.3.1.2   *Sleep Initiation*

Regions associated with sleep initiation include subcortical structures, such as brainstem, hypothalamus, basal ganglia and basal forebrain (Dang-Vu et al., 2010; Maquet, 2000; Szymusiak, Gvilia, & McGinty, 2007; H. P. Van Dongen, Belenky, & Krueger, 2011). In addition, some cortical regions are sensitive to the involuntary homeostatic drive to sleep, such as orbital, medial and dorsolateral prefrontal cortex and medial parietal cortex (Dinges & Kribbs, 1991; Krueger, Huang, Rector, & Buysse, 2013; Maquet, 2000).

Sleep-wake status is regulated by a two neurocognitive processes: a homeostatic process and a circadian process. The homeostatic process determines the sleep homeostatic pressure that drives sleep. The circadian process modulates the circadian rhythm that adjusts wakefulness. The interaction between these two processes drives the switch between sleep and wakefulness and the stability of waking neurocognitive function.

Basal ganglia may play an important role in such sleep-wake regulation. Reduced activation in basal ganglia is reported (Kaufmann et al., 2006) in non-rapid eye movement sleep (NREMS). In addition, reduced wakefulness and robust fragmentation of sleep-wake behavior is observed in rats with striatal (caudoputamen) lesions (Qiu, Vetrivelan, Fuller, & Lu, 2010). Hypothalamus is associated with circadian process. It is reported to engage in generation of circadian rhythm (R. Y. Moore, 1995) and has influences on subcortical structures (Saper, Scammell, & Lu, 2005). Based on online brain atlas reconciliation tool, both basal ganglia and hypothalamus are contained in sub cortical gray nuclei in AAL atlas system. In addition, sleep regulations has effect on other cortical regions' activities. Reduction of activity is reported in higher level cortical regions, such as prefrontal cortex, parietal cortex, and anterior cingulate in NREMS (Dang-Vu et al., 2010; Maquet, 2000). Interactions between basal ganglia or other subcortical structures and higher-level cortical regions, such as frontal and parietal lobe, represent the perturbations from sleep to waking neurocognitive functions.

5.3.1.3 Top-Down Modulation

Regions involved in top-down attention control principally locates in frontal parietal lobe, including medial frontal and parietal cortices, superior parietal cortex, lateral precentral gyrus, frontal eye field, posterior parietal cortex and intraparietal sulcus (Bressler et al., 2008; Corbetta & Shulman, 2002; T. Moore & Armstrong, 2003). Based on online brain atlas reconciliation tool, regions involved in top-down attention networks locate lateral frontal lobe, medial frontal lobe, lateral parietal lobe and medial parietal lobe. Such attention network interacts with other cortical regions in order to support visual attention function. Correlated regions mainly locate in visual cortex, such as primary visual cortex and extrastriate cortex (Bressler et al., 2008; Corbetta,

Kincade, & Shulman, 2002; Itti & Koch, 2001; Kastner & Pinsk, 2004; T. Moore & Armstrong, 2003; Schroeder, Mehta, & Foxe, 2001). Correlated regions also include subcortical areas.

In top-down control, attention is modulated from the higher level brain areas to lower level brain areas. Higher level brain areas refer to brain regions engaged in higher cognitive process. Frontal lobe is critical in neural structural model subserving the executive neurocognitive function, such as decision making and emotional regulation. Cognitive level of region-of-interests in this research was shown in Figure 19. Higher level regions were labeled with bold fronts. Lesions in frontal lobe are found relevant to impairment performance in decision making tasks (Bechara, Damasio, & Damasio, 2000; Bechara & Van Der Linden, 2005; Fellows & Farah, 2005). Parietal lobe is found essential to serve neurocognitive functions involved with self-awareness and spatial localization and attention orienting (Hopfinger, Buonocore, & Mangun, 2000; Itti & Koch, 2001Krueger, 2013 #123; Vossel et al., 2012). In addition, superior parietal may play an important role in corporation of goal-oriented attention modulation to stimuli-driven attention modulation since due to its activation in both endogenous and exogenous attentional shifts, while superior frontal lobule has only been reported subserving in spatial shifting of attention (Corbetta, Miezin, Shulman, & Petersen, 1993). Moreover, the ability of neurocognitive function is also determined by the interactions within top-down attention networks and between such networks and their correlated regions. Pathways are found among frontal lobe, parietal lobe, temporal lobe and visual cortex, especially intermediate-tier areas (VP, V4).

5.3.1.4 Sensory Processing

Key brain structural regions, serving in sensory processing function, include inferior occipital lobe (Chee & Chuah, 2007; Chee et al., 2008) and extrastriate areas (Purves, 2008; Purves et al., 2001). Based on online brain atlas reconciliation tool, brain structural model involved in sensory processing locate principally in lateral occipital lobe and medial and inferior occipital lobe.

When performing a visual cognitive task, the environmental stimuli information is first projected onto primary visual cortex and then progresses along a dorsal pathway that leads to parietal lobe (Itti & Koch, 2001; Purves, 2008) for further processing in biasing selection of visual information and spatial attention shifting (Haxby et al., 1991; Moran & Desimone, 1985; Purves, 2008; Purves et al., 2001).
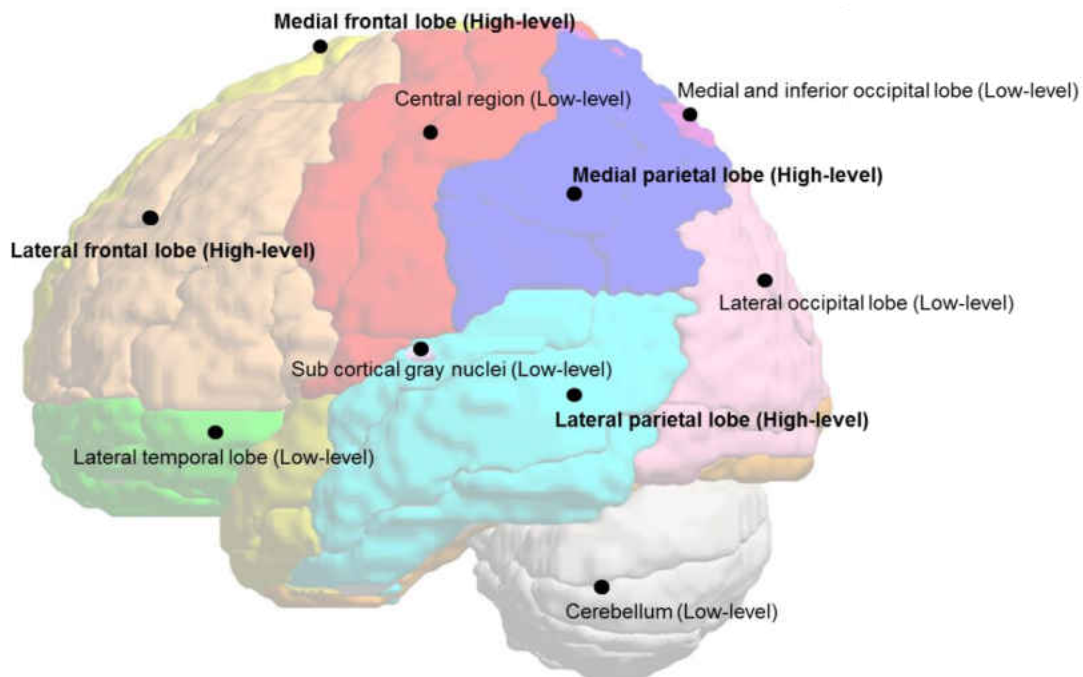

Figure 19 Higher versus Lower Cognitive Level Region-of-Interests

5.3.1.5 Working Memory

Key brain structural model associated with working memory include inferior temporal cortex, middle temporal cortex, middle superior temple cortex, fusiform (Courtney, Ungerleider, Keil, & Haxby, 1996; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999; Ungerleider & G, 2000). Based on online brain atlas reconciliation tool, brain structural model involved in sensory processing is mostly contained in lateral temporal lobe in AAL atlas system.

Visual information transferring along a dorsal pathway to temporal lobe involves in visual short-term memory. The ability to retrieve working memory is determined by the interactions between temporal lobe and top-down attention networks as well as visual cortex. Such interactions allow representation of visual objects and its recognition by retrieving visual spatial infromation, and therefor support a biasing selection of sensory information (Kastner & Pinsk, 2004; Luck & Vogel, 1997) and a motion of attention shifting (Purves, 2008). Additionally, fusiform is reported engaging in sensory processing in the context of facial information working memory (Courtney et al., 1996).

5.3.1.6 Subcortical areas and Cerebellum

Subcortical areas associated with attention control include thalamus and hippocampal. Cerebellum contains of vermis and cerebellar structures, such as crus I, cerebellar crus II, lobules V, lobules VI, lobules VIII, and lobules VIIa (O'Reilly, Beckmann, Tomassini, Ramnani, & Johansen-Berg, 2010). Based on online brain atlas reconciliation tool, these subcortical areas refer to sub cortical gray nuclei in AAL atlas system, while cerebellar structures refer to Cerebellum.

Subcortical areas globally coordinate over the entire brain to support neurocognitive functions (Saper et al., 2005). Additionally, subcortical structure is widely reported in serving spatial attention control from neuroimaging studies (Corbetta et al., 1993; Gitelman et al., 1999; Hopfinger et al., 2000; Yoo et al., 2007). The ability to maintain wakefulness and perform cognitive functions depends on the interaction between subcortical areas to other cortical areas. A reduction of such connectivity refers to reduced self-awareness and attentional focus on task and hence refers that brain is involuntarily driven to fell asleep (Saper et al., 2005).

One popular hypothesis about the neurocognitive function of cerebellum is the control of involuntary motion (Miall & Wolpert, 1996). However the observation (Clower, Dum, & Strick, 2005; Clower, West, Lynch, & Strick, 2001; Middleton & Strick, 2001) of directed influence from cerebellar structure to prefrontal and posterior parietal cortex supports another hypothesis (Bower, 1997) that the main function of cerebellum is subserving in sensory processing rather than simple motional reflex. Another observation (O'Reilly et al., 2010) has been reported that cerebellum contains a supramodal zone, including lobules VIIa, cerebellar crus I and II. This model connects with high level cognitive brain areas, such as dorsolateral prefrontal cortex and the frontal pole, and the inferior parietal lobule, instead of the brain areas which directly serves in sensory processing. Such observation also brings additional evidence to the hypothesis that cerebellum is not directly involved in motor control, but in subserving higher level cognitive function which modulate sensory processing to motor control.

5.3.2 Comparison of Effective Connectivity Networks

Effective connectivity networks established through my approach varies between the SD and the RW condition, which could be evidence that sleep deprivation has an impact on how brain works to perform the same visual sustained-attention task. First, sleep deprivation may bring influence on the reduction of brain functional integration between segregated brains areas, since the majority of links in effective connectivity network in RW are bidirectional, while most of effective connectivity are directed from one area to another as in SD. Second, brain may generate higher effective connectivity level to maintain the task performance in SD, since the strength of Granger causal influence between pairs of ROIs are higher in SD than in RW.

5.3.2.1 Rest-wakeful Condition

In RW condition, most connectives are bidirectional, which formulates feedback pathways across important brain areas involved in attentional top-down modulation, including lateral frontal lobe, medial frontal lobe, lateral parietal lobe, and medial parietal lobe and sub cortical gray nuclei, as shown in Figure 20. The first four brain areas are widely studied as the frontal-parietal cortex in attentional top-down modulation (Bressler et al., 2008; Itti & Koch, 2001; Theeuwes, 2010). Frontal lobe is involved in higher cognitive processing, especially decision-making (Yang & Raine, 2009). Parietal lobe plays an important role in spatial localization, attention orienting and coordination with bottom-up modulation (Itti & Koch, 2001). Basal ganglia are the main structures in sub cortical gray nuclei area. Directed Granger causal influences in the model of brain effective connectivity in RW was shown in Figure 21. Projects from cortical areas to basal ganglia refers to a process of global coordination of excitation of

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cortical neurons and movement inhibition and initiation (Purves, 2008). Granger causal influence

from lateral occipital lobe to medial frontal lobe could be engaged in the process in which visual

information was forwarded to higher order cortical areas for further processing. Lateral temporal

lobe serves an important role in working memory. The Granger causality influence from medial

frontal lobe and lateral parietal lobe retrieval to lateral temporal lobe can be interpreted as the

executive control order in memory retrieval (Tomita et al., 1999). Thus, effective connectivity,

while performing visual sustained-attention task, in RW demonstrates a brain functional

integration dominated by Goal-oriented attentional control, mediated via visual information

processing, and storage and retrieval of working memory.

![Brain diagram showing bidirectional pathways. Labels: Medial frontal lobe, Central region, Medial and inferior occipital lobe, Medial parietal lobe, Lateral frontal lobe, Lateral occipital lobe, Sub cortical gray nuclei, Lateral parietal lobe, Lateral temporal lobe, Cerebellum.]
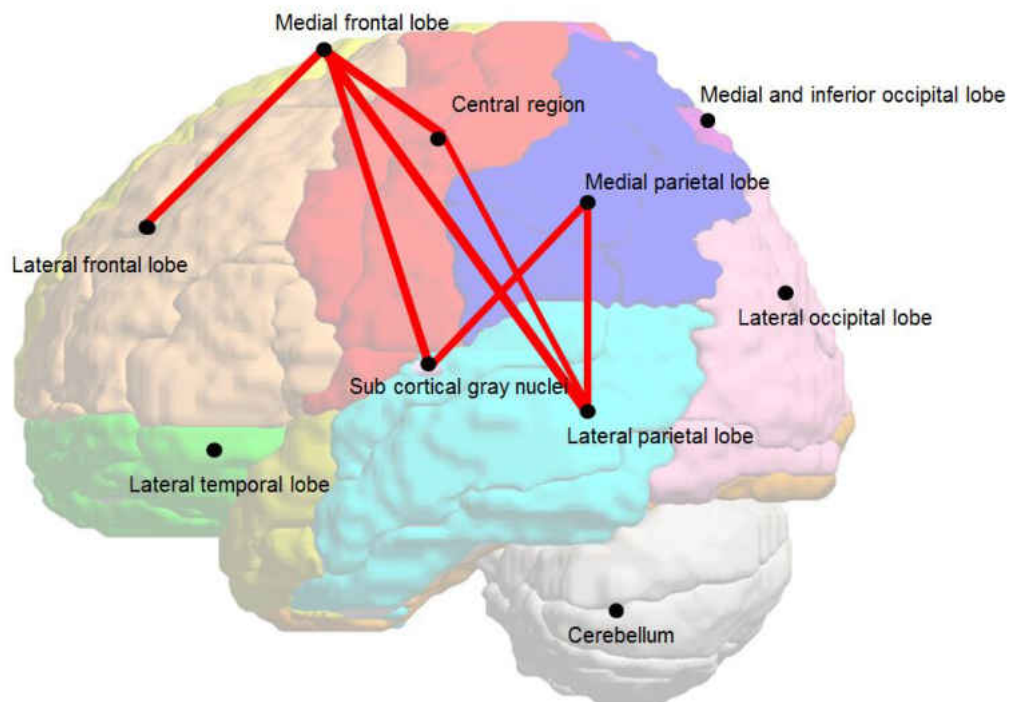
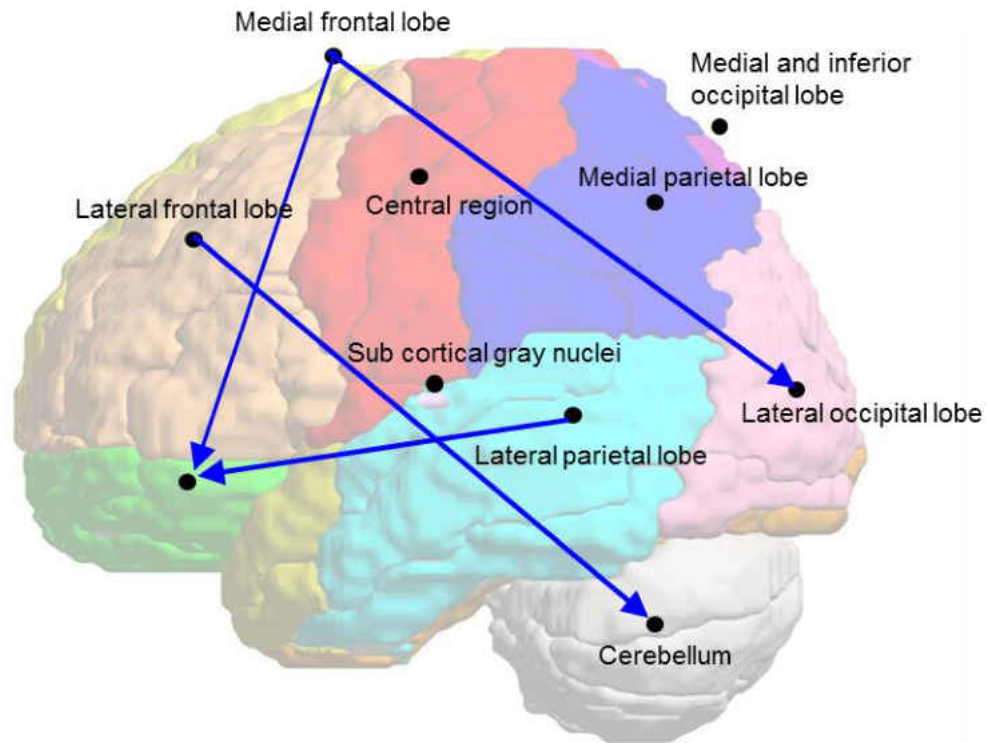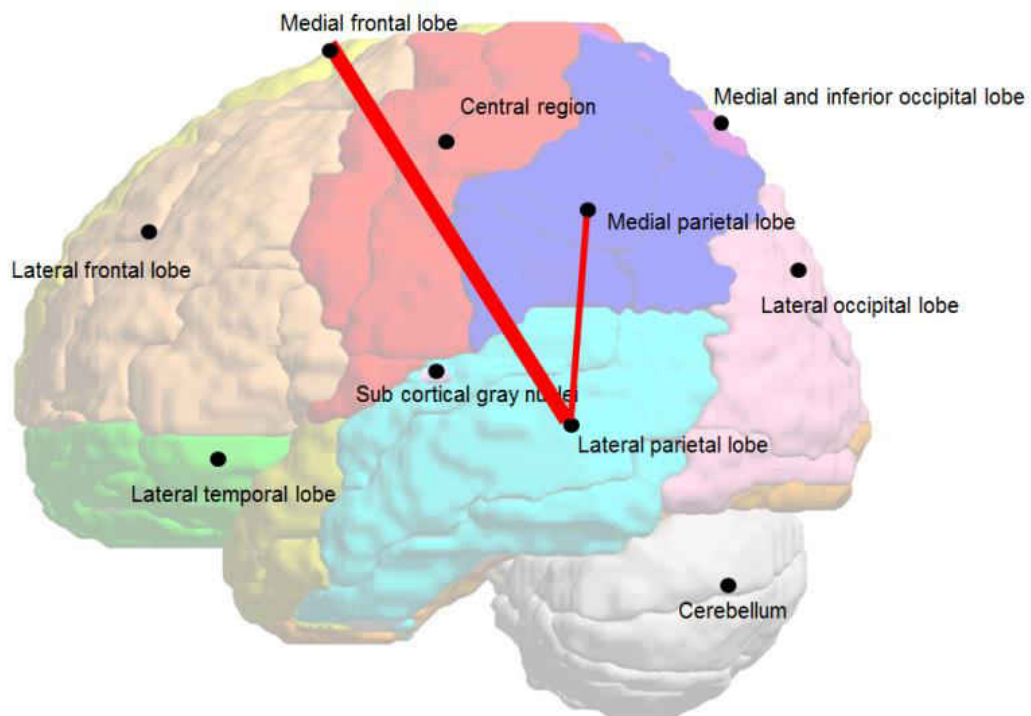Figure 20 Bidirectional Pathways in the Model of Brain Effective Connectivity in Rest Wakefulness

Figure 21 Directed Causal Influences in the Model of Brain Effective Connectivity in Rest Wakefulness

5.3.2.2   *Sleep-deprived condition (SD)*

In the SD condition, the amount of bidirectional connectivity decreased to two: one between medial frontal lobe and lateral parietal lobe; the other between medial parietal lobe and lateral parietal lobe, as shown in Figure 22. The bidirectional connectivity between frontal lobe and parietal lobe indicated that both *top-down* control and *bottom-up* control determine the shifting of attention (Itti & Koch, 2001). There were two groups of directed connected structure in the SD condition, as shown in Figure 23. Within the first group, the medial frontal lobe were a hub which receives influences from 5 other areas, including the lateral frontal lobe, sub cortical gray nuclei, central region, lateral occipital lobe and medial and inferior occipital lobe. This

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might be the evidence that attention was determined by bottom-up modulation in the SD condition, since areas related to local stimuli processing exerted directed influences to higher-order cognitive area. Moreover, another hub in effective connectivity network in the SD condition was the cerebellum. The cerebellum is thought to be engaged in sensory processing, which serves higher cognitive activity respondent to stimuli (O'Reilly et al., 2010) and in decision-making of attentional reorienting (Strick, Dum, & Fiez, 2009). While performing visual sustained-attention task in SD condition, the cerebellum receives influences from 8 other brain areas out of a total 9 other brain areas. Directed influence from frontal parietal lobe might be the evident that visual-spatial attention is determined by stimuli-driven modulation in SD.

Figure 22 Bidirectional Pathways in the Model of Brain Effective Connectivity in Sleep Deprivation
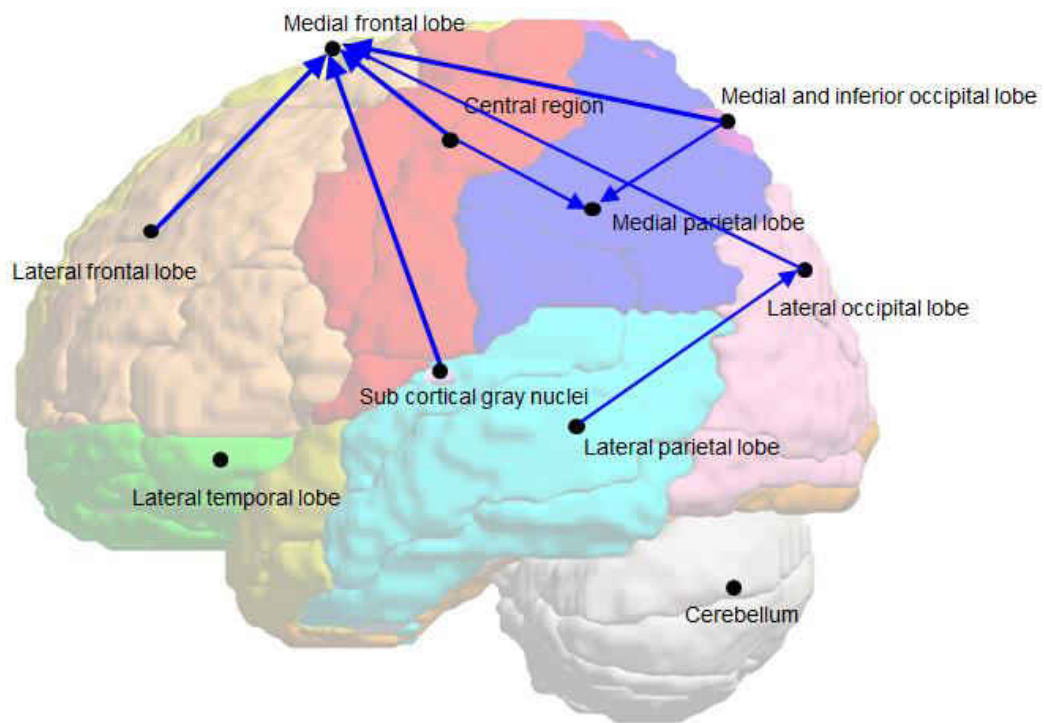
Figure 23 Directed Causal Influences in the Model of Brain Effective Connectivity in Sleep Deprivation

5.3.3 Residual Network

The increases of Granger causal influences after sleep deprivation, shown in Figure 24, may be related to increases of functional integration in certain neurocognitive modulations to maintain the visual sustained-attention task, shown in Table 15.

Table 15 List of Increased Granger Casual Influence after Sleep Deprivation and their Effected Neurocognitive Modulations

Neurocognitive Modulations	Increased Granger Causal Influences after Sleep Deprivation
Task-related attentional orienting	i. Lateral frontal lobe→Cerebellum ii. Subcortical gray nuclei→Cerebellum
Sensory processing and retrieval of working memory	i. Medial and inferior occipital lobe→Medial frontal lobe ii. Lateral temporal lobe→Cerebellum
Salience-driven attentional shifting	i. Lateral parietal lobe→Medial frontal lobe ii. Medial parietal lobe→Cerebellum iii. Lateral parietal lobe→Cerebellum iv. Medial and inferior occipital lobe→Cerebellum
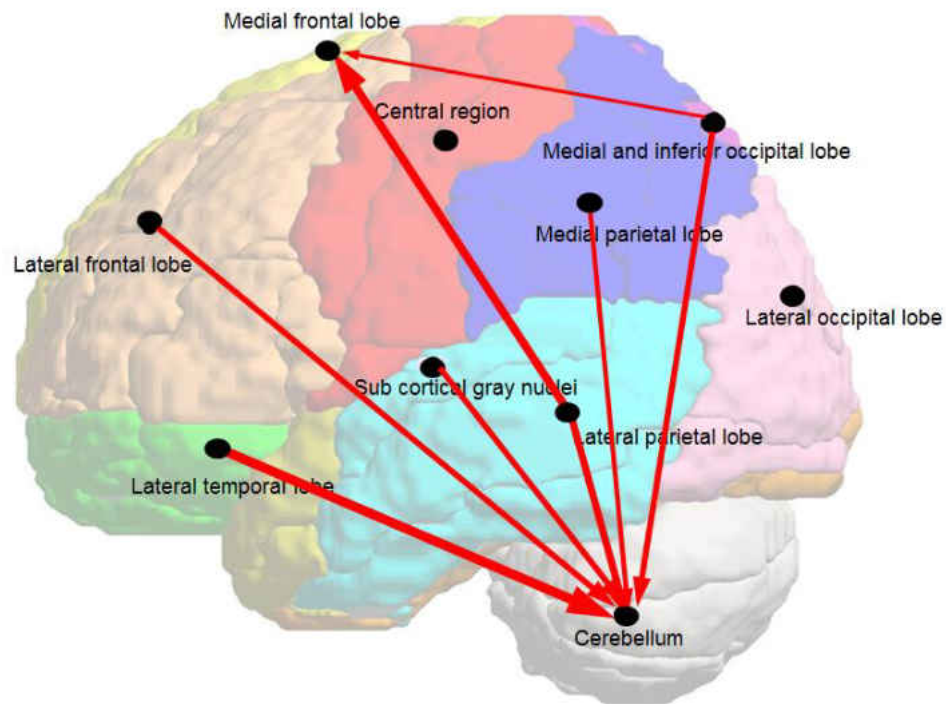
Figure 24 Granger Causal Influences Stronger in Sleep-deprived Condition

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Granger causal influences between some pairs of brain areas decreased after sleep

deprivation, shown in Figure 25. This reduction of Granger causal influences may be related to

changes of functional integration in some neurocognitive modulations to initiate sleep. Those

modulations related to reduced Granger causal influences after sleep deprivation was shown in

Table 16.

Table 16 List of Reduced Granger Casual Influence after Sleep Deprivation and their Effected
Neurocognitive Modulations

| Neurocognitive Modulations	Reduced Granger Causal Influences after Sleep Deprivation	
Increased involuntary homeostatic drive to sleep	i.	Subcortical gray nuclei→ Lateral parietal lobe
	ii.	Subcortical gray nuclei→Medial parietal lobe
Reduced self-alertness/awareness	i.	Medial parietal lobe→Lateral frontal lobe
	ii.	Medial parietal lobe→Lateral temporal lobe
Reduced focus on task's goal	i.	Medial frontal lobe→Lateral occipital lobe
	ii.	Medial frontal lobe→Subcortical gray nuclei
	iii.	Medial parietal lobe→Subcortical gray nuclei
Attenuation of visual processing	i.	Lateral temporal lobe→Subcortical gray nuclei
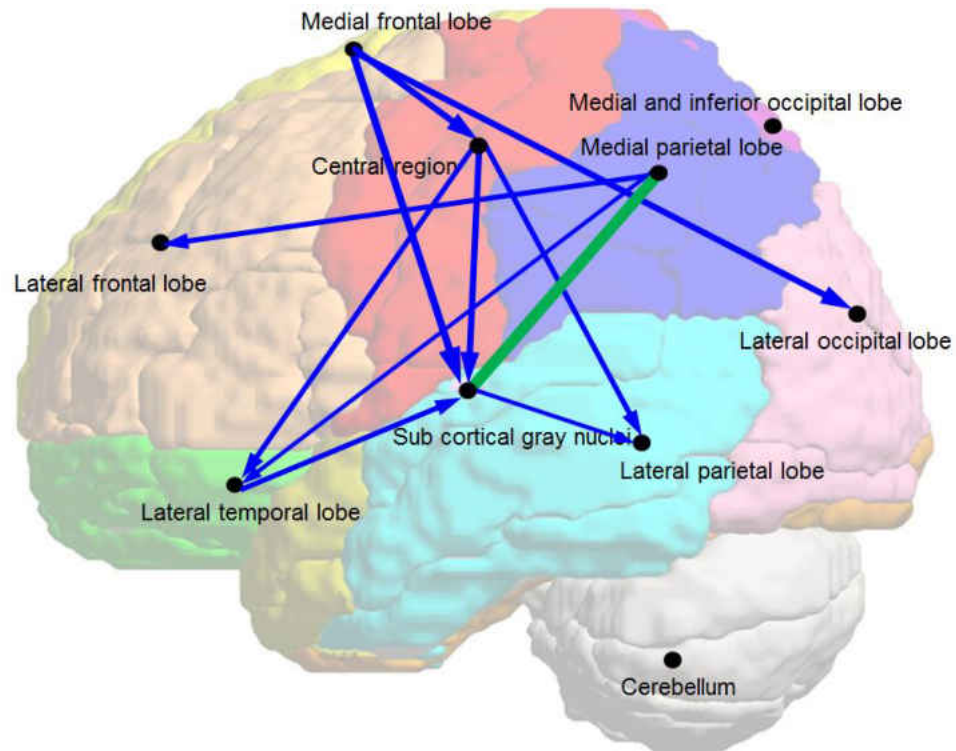
Figure 25 Granger Causal Influences Weaker in Sleep-deprived Condition

Residual network analysis demonstrated that there are stronger Granger causal influences in the SD condition between pairs of areas engaged in maintaining attention on the task. Additionally, there were weaker Granger causal influences in the SD condition between pairs of areas serving in Sleep-initiation cognitive processes. Sleep deprivation triggered competition between maintaining attention on the task and switching from wakefulness to sleep, which could lead to higher variation of task performance.

CHAPTER 6: PHASE III LINK CHANGES OF BRAIN ACTIVITY TO CHANGES OF RESPONSE TIME

Task followed by identifying the pattern of functional difference when performing sustained-attention tasks in the RW condition and in the SD condition, a question emerged: how would this pattern related to the decrease of response time induced by sleep deprivation, which was found in Phase I? To answer this question, brain connectivity was linked to response time by assessing the relationship between residual Granger causal influences and residual response times between sleep-deprived condition and rest-wakeful condition.

6.1 Methods

To analyze the relationship between residual response time and residual Granger causal influence, a four-step Spearman rank correlation analysis was applied. This was adjusted based on the procedures used in electrophysiological studies (Mo et al., 2011; Wen et al., 2012; Zhang et al., 2008). This procedure has been verified effective to correlate task performance with Granger causality. First, for each subject, residual response time was calculated, which was defined as the difference of response time between in the RW condition and in the SD condition (RT_{RW}-RT_{SD}). Second, residual response time were normalized into t scores and sorted in an ascending order from low to high. Due to the missing sessions in the task data, 3 sessions were removed were included in this analysis for each subject and in each condition. The rest 10 sessions were segmented into 9 groups, where every 3 consecutive sessions were formed into one group. Residual response time t scores were averaged within each group and then across

subjects. Third, for each pair of brain areas, residual Granger causal influence, which is the difference of Granger causal influence between in RW condition and in SD condition (F_{RW}-F_{SD}), was calculated for each session, sorted as the rank of residual response time t scores and averaged within each group and then across all subjects, and transformed into t scores. Fourth, the population level residual Granger causal influence t-score of each response time group was plotted as a function of the mean residual response time t-score. Thereafter, Spearman rank correlation was calculated to assess the relation between these two variables.

6.2   Results

The 20 strongest residual Granger causal influences found in Phase II were included in the assessment of relation between residual response time and residual Granger causal influence. Spearman rank correlations between selected residual Granger causality and residual response time were sorted in in term of an ascending order in the term of their absolute value, shown in Table 17. Additionally, positive (in red) and negative (in blue) correlations between residual Granger causality and residual response time were demonstrated on the neuroanatomical map in Figure 26.

Table 17 Spearman Correlations between Residual Granger Causality and Residual Response

Time

Regions Exerting Causal Influences	Regions Receiving Causal Influences	Correlations Between Residual Granger Causality and Residual Response Time
MF	CR	-0.25
MIO	MF	-0.317
LP	CB	-0.333
CR	LT	-0.433
SC	LP	-0.433
CR	LP	-0.483
SC	CB	-0.483
MIO	CB	-0.517
LF	CB	-0.55
CR	SC	-0.583
LP	MF	-0.617
LT	CB	-0.633
MP	LT	-0.65
LT	SC	-0.667
MF	LO	-0.683
MF	SC	-0.717
MP	CB	-0.733
MP	SC	-0.867
SC	MP	0.017
MP	LF	0.533
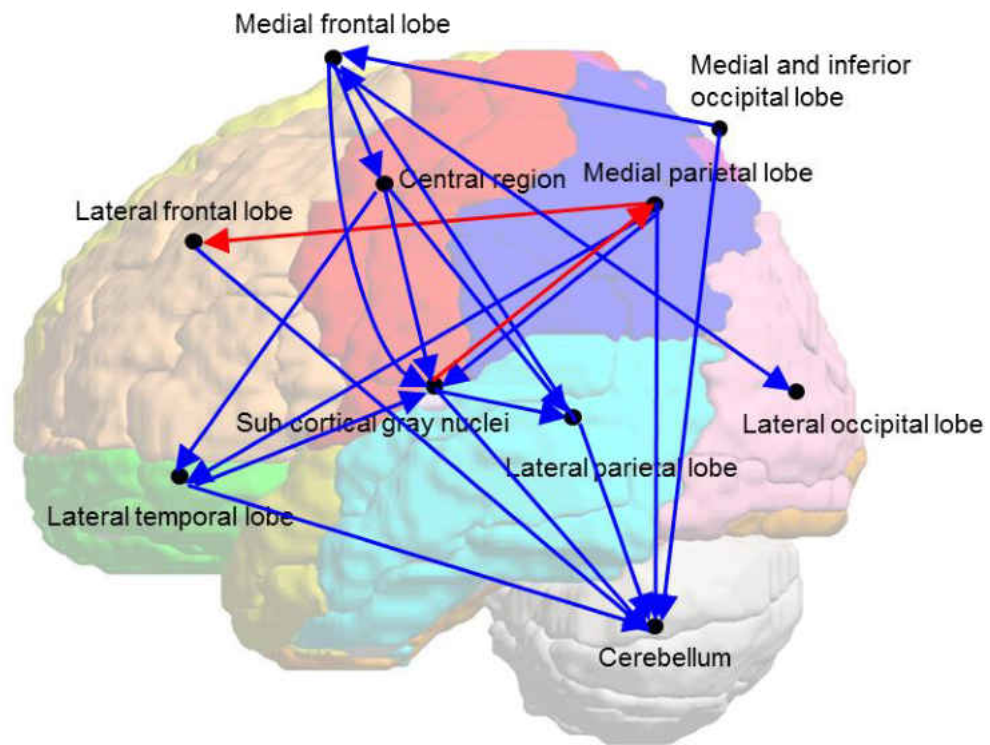
Figure 26 Positive (Red) Spearman Rank Correlations and Negative (Blue) Spearman Rank Correlation between Residual Granger Causality and Residual Response Time

There were three significant correlations. Each represents a significant association relationship between residual Granger causal influences between one pair of brain areas and residual response time. The three pairs of causal influences included: medial frontal lobe → sub cortical gray nuclei, medial parietal lobe → cerebellum, and medial parietal lobe → sub cortical gray nuclei. The other results of correlation analysis about the rest 17 residual Granger causality were shown in Appendix B.

In the analysis, the residual RT scores were multiplied by -1 before correlation analysis so that larger residual RT score indicates longer response time in the SD condition. Thus, the x axis in the plot of residual Granger causal influence and residual response time represents the difference of response time between SD and RW conditions, while y axis represents the difference of Granger causal influences between RW and SD conditions. A larger value along x axis referred to longer response time in SD. A larger value along y axis referred to weaker strength of causal influence in SD.

- Medial frontal lobe → sub cortical gray nuclei

The plot of residual Granger causal influence t-score as a function of residual RT t-score is shown in Figure 27. RHO refers to spearman correlation coefficient, while PVAL refers to significance level of RHO. Residual Granger causal influence in the direction, medial frontal lobe → sub cortical gray nuclei, was negatively correlated with residual response time (rho = -0.717, p = 0.037 < 0.05). This indicates that the stronger the medial frontal lobe Granger causes were to the sub cortical gray nuclei in the SD condition, the longer participants took to respond to the target stimuli and vice versa.

Based on Phase II results, the Granger causal influence from the medial frontal lobe to the sub cortical gray nuclei got weaker in the SD condition, which indicates shorter response time while sleep deprived.
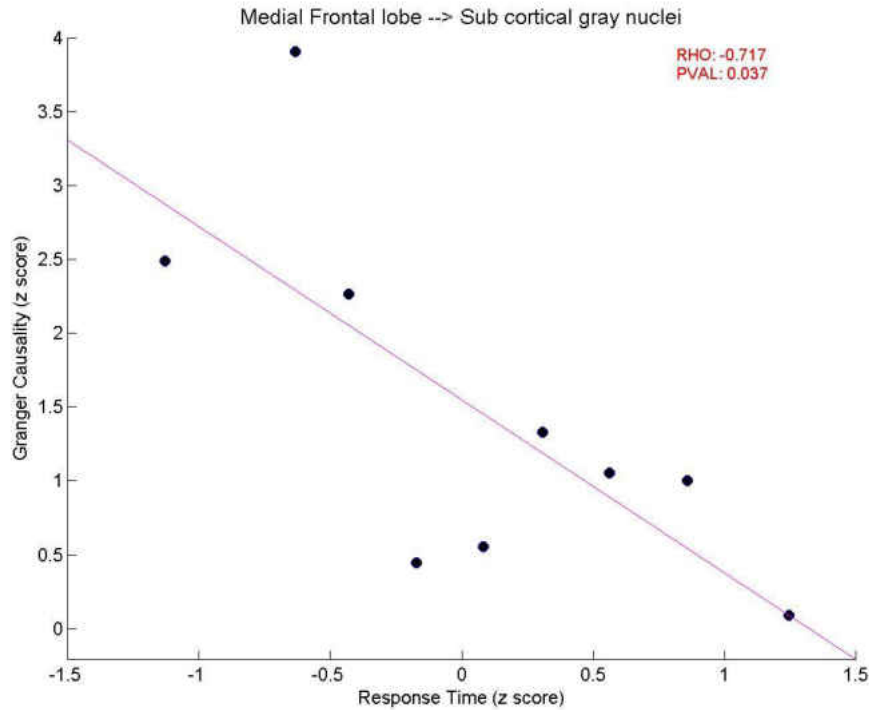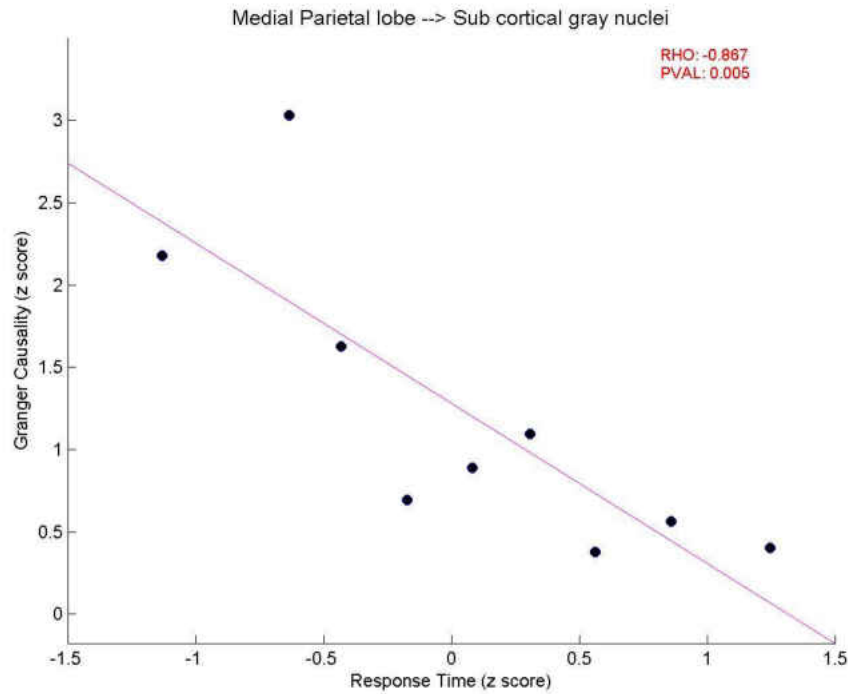

Figure 27 Spearman Rank Correlation: Medial Frontal Lobe -> Sub Cortical Gray Nuclei

- Medial parietal lobe → sub cortical gray nuclei

The plot of residual Granger causal influence t-score as a function of residual RT t-score is shown in Figure 28. Residual Granger causal influence in the direction, medial parietal lobe → sub cortical gray nuclei, was negatively correlated with residual response time (rho = - 0.867, p = 0.005 < 0.05). This indicates that the stronger the medial parietal lobe Granger causes sub cortical gray nuclei in SD, the longer taken to respond to target in SD and vice versa.

Based on Phase II results, the Granger causal influence from medial parietal lobe to sub cortical gray nuclei gets weaker in SD, which therefor indicates shorter response time in SD.

Figure 28 Spearman Rank Correlation: Medial Parietal Lobe -> Sub Cortical Gray Nuclei

- Medial parietal lobe → cerebellum

Plot of residual Granger causal influence t-score as a function of residual response time (RT) t-score is shown in Figure 29. Residual Granger causal influence in the direction, medial parietal lobe → cerebellum, is negatively correlated with residual response time (rho = - 0.733, p = 0.031 < 0.05), meaning that the stronger medial parietal lobe Granger causes cerebellum in SD, the longer taken to respond to target in SD, and vice versa.

Based on Phase II results, the Granger causal influence from medial parietal lobe to cerebellum gets stronger in SD, which therefor indicates longer response time in SD. In other words,
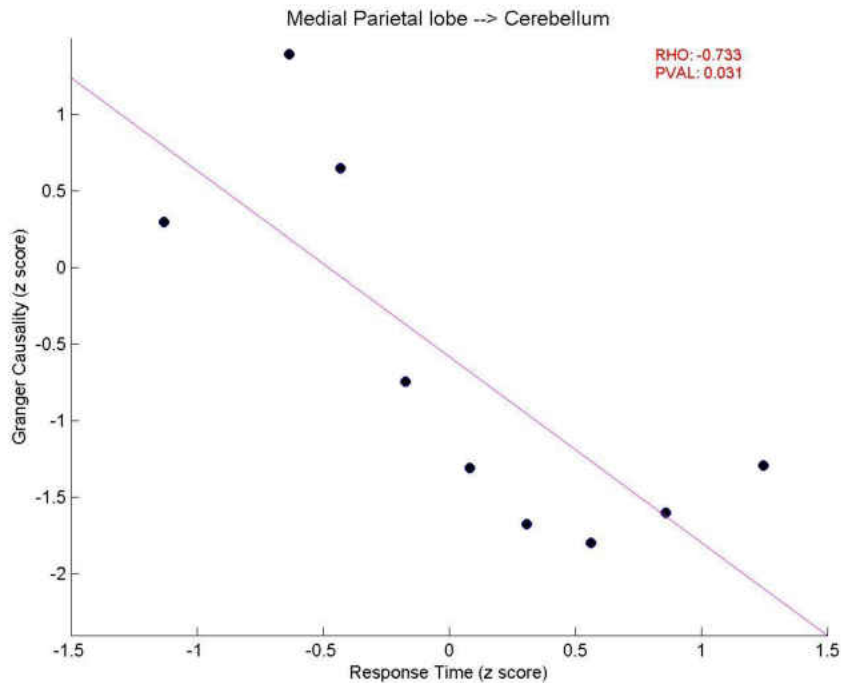
Figure 29 Spearman Rank Correlation: Medial Parietal Lobe -> Cerebellum

6.3   Discussions

Based on pair-t test in Phase I, population level mean response time is shorter in the SD condition. On the other hand, analysis of correlation between residual Granger causal influence and residual response time demonstrated reduction of Granger causal influences induced by sleep deprivation, as shown in Figure 30, in the directions: medial frontal lobe → sub cortical gray nuclei and medial parietal lobe → sub cortical gray nuclei, predict shorter response in the SD

condition, while increases of Granger causal influence in the direction, the medial parietal lobe

→the cerebellum, predicts longer response time in SD. Granger causal influences were shown in

red when changes of their strength correlated with shorter response time, and in blue when

correlated with longer response time. Thus, influences driven from the frontal parietal lobe to the

sub cortical gray nuclei might play a more dominant role for visual sustained-attention task in

SD, since their predictions of changes of response time match with the actual change of response
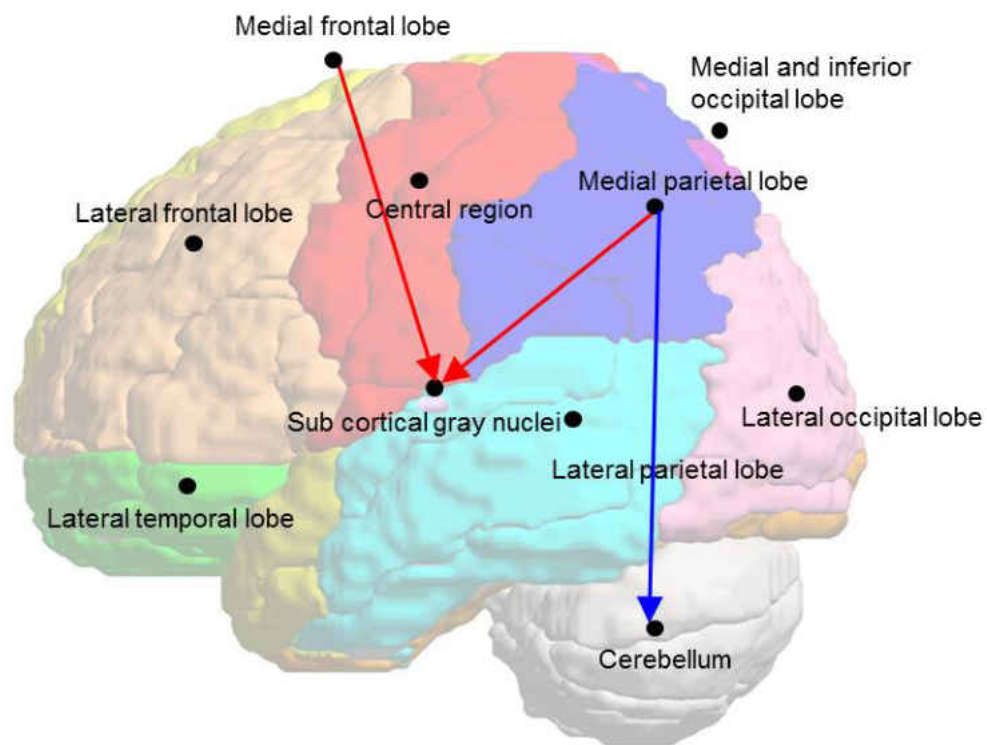
time.

Figure 30 Changes of Effective Connectivity Predict Changes of Response Time

CHAPTER 7: CONCLUSION

This research discussed the impact of sleep deprivation on behavior performance, pattern of brain activity and the correlation relationship between brain activity and behavior performance. Results confirmed significant difference of attention lapsing between full rest and sleep deprivation. Additionally, this research revealed that the integration of top-down control and bottom-up attentional modulations determined attention shifting in sleep deprivation, while top-down control plays an dominant role in attention orienting in rest-wakeful condition. Moreover, this study identified three pairs of connectivity patterns correlated with the changes of performance induced by sleep deprivation. The Granger causal influences, from medical frontal lobe to sub cortical gray nuclei and from medial parietal lobe to sub cortical gray nuclei, serve as indictors of reduction of response time induced by sleep deprivation. The Granger causal influence, from medial parietal lobe to cerebellum, serves as a predictor of increase of response time induced by sleep deprivation.

The short window Granger causality approach used in this study is an exploratory method, which has several advantages:

- Mapping the directed effective connectivity over the entire brain
- Investigating the dynamic causality structure in Granger causality analysis
- Providing larger measures of Granger influence exerted from brain area to another than classic Granger causality approach

A few topics can be included in the future research. First, multivariate Granger causality analysis should be applied to investigate the partial Granger causal influence between selected brain regions. The basic concept of the current approach is Granger causality mapping, which

may yield spurious causal influences when two brain areas are jointly mediated by another one. Multivariate Granger causality, conditional Granger causality or partial Granger causality can be applied to address this issue. Second, due to the trial-by-trial experiment design, the effect of sleep deprivation on different tasks (incongruent and congruent visual attentional tasks) could not be investigated in the current work. Thus, in further research, sustained-attention tasks could be conducted in a block design experiment to address the understanding of the effect of sleep deprivation on different visual-spatial tasks. Third, another interesting topic is to study on vulnerability of the effect of sleep deprivation. The ability to main stable neurocognitive performance following sleep deprivation may vary among population. Such observation may indicate inter-individual difference in brain causal interaction induced by sleep deprivation. Fourth, the relation between task performance and functional pattern could be investigated with consideration of subjects' vulnerability to sleep deprivation. Fifth, insights could be gained about how the brain adapts to sleep deprivation for various senses by studying a similar task for different senses. The current model can be validated if similar influences could be detected in brain regions expected for audio processing in response to an audio based task. Sixth, various discrimination tasks can be used to further develop and understand Ganger influences and process connections in the brain. That is, instead of testing response time for visual stimuli, participants would be asked to respond only to specific kinds of stimuli among a variety of stimuli.

APPENDIX A:
SUBJECT-LEVEL EFFECTIVE CONNECTIVITY MODEL
IN THE SLEEP-DEPRIVED CONDITION AND IN THE REST-
WAKEFUL CONDITION
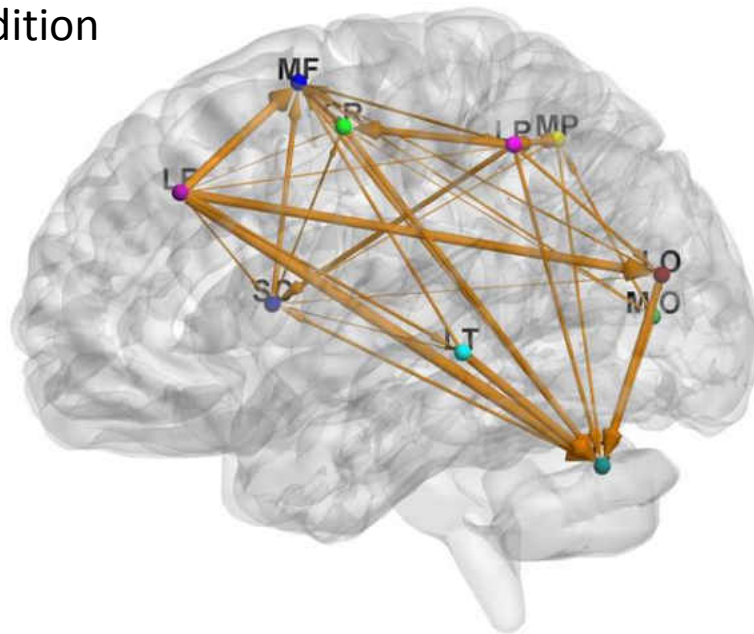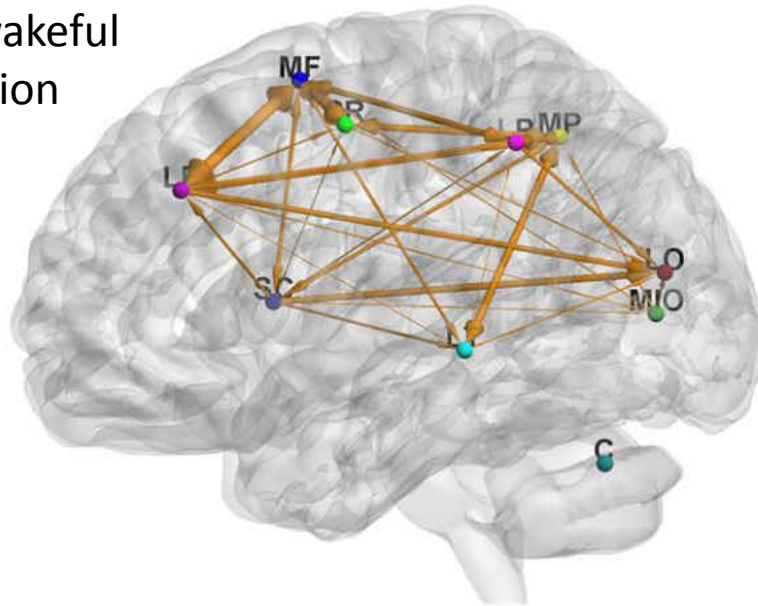
Rest-wakeful
Condition
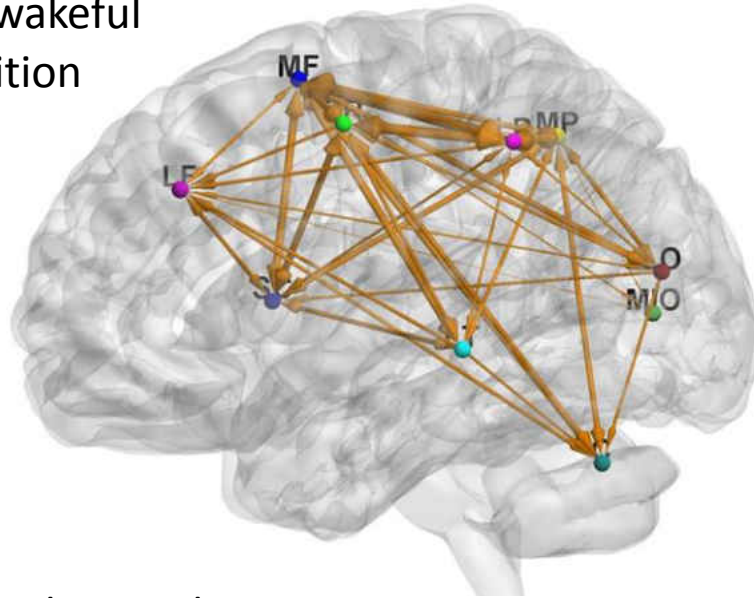
Sleep-deprived
Condition

Figure 31 Subject 1: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)
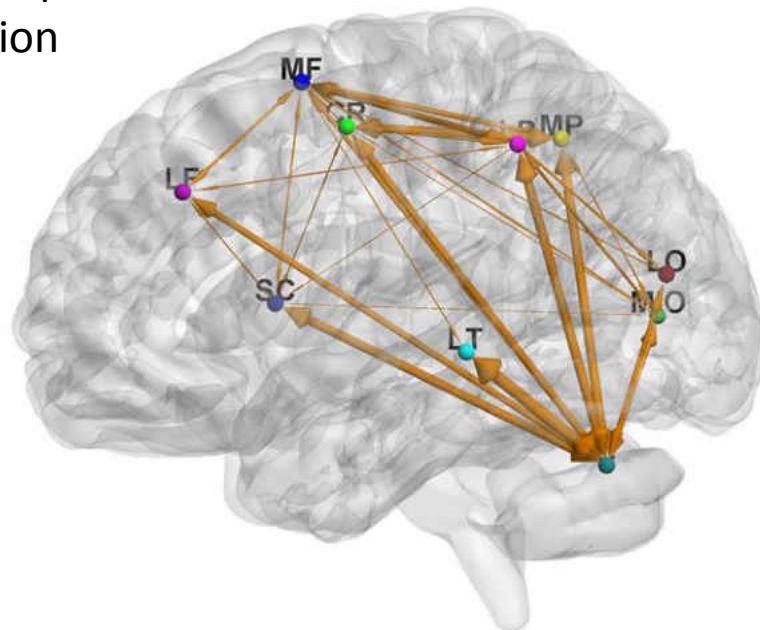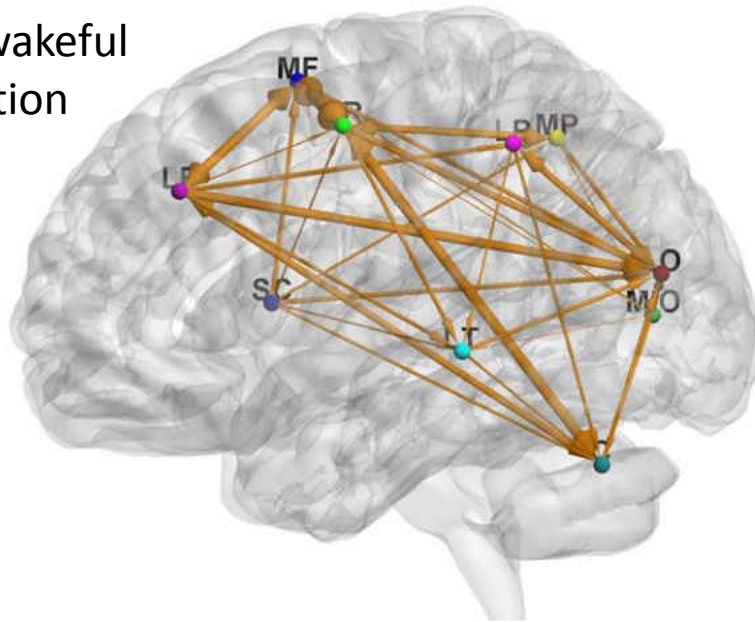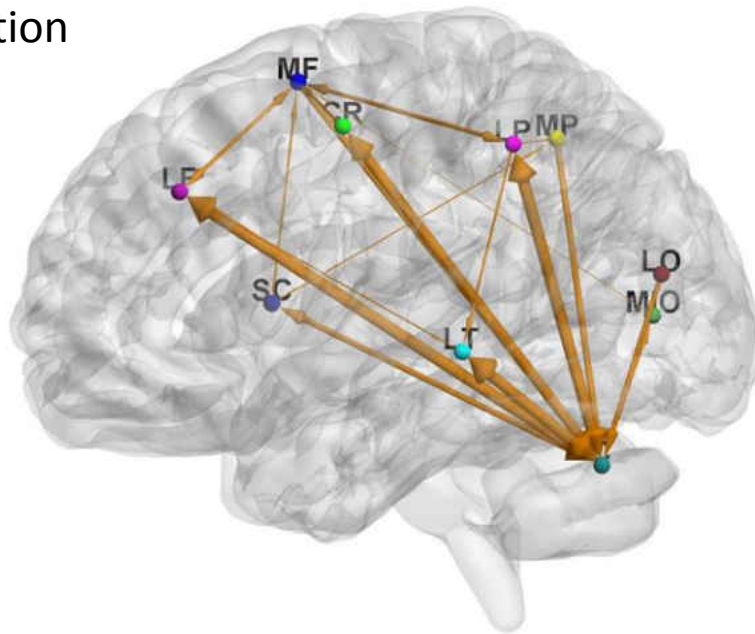
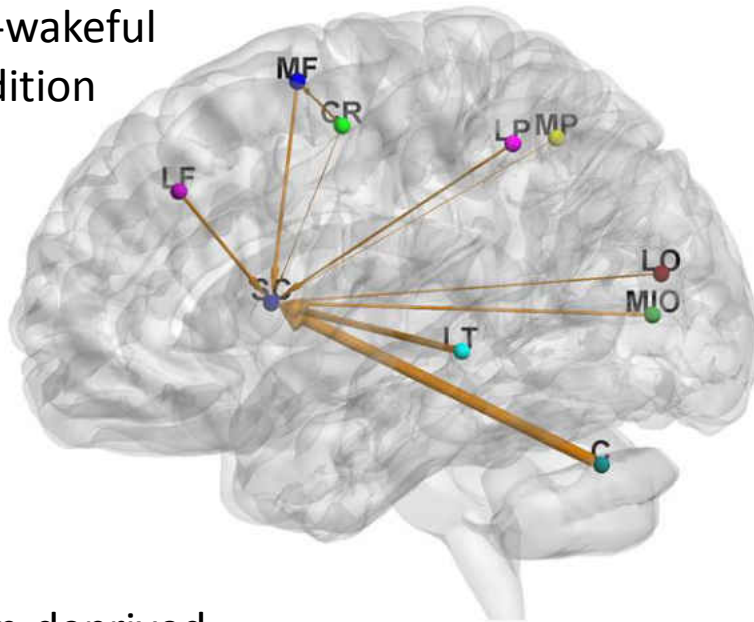Rest-wakeful
Condition

Sleep-deprived
Condition

Figure 32 Subject 2: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

98

Rest-wakeful
Condition

Sleep-deprived
Condition

Figure 33 Subject 3: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

Rest-wakeful
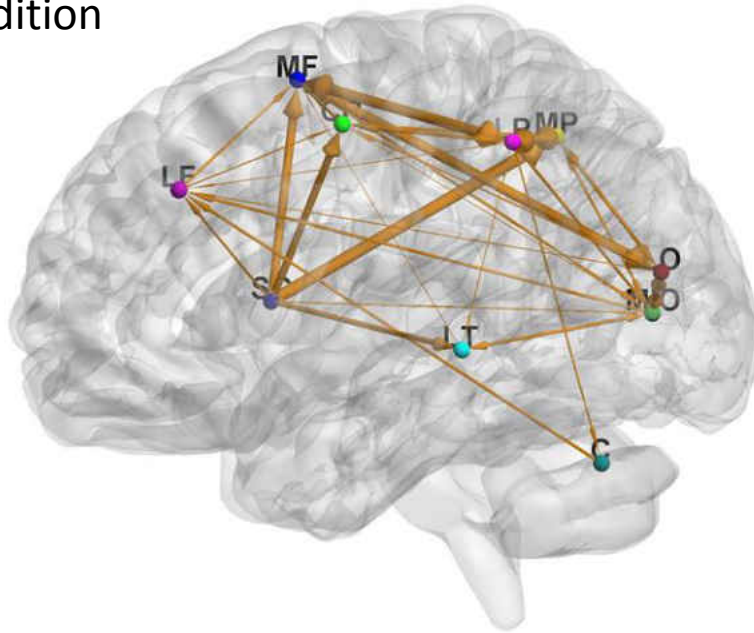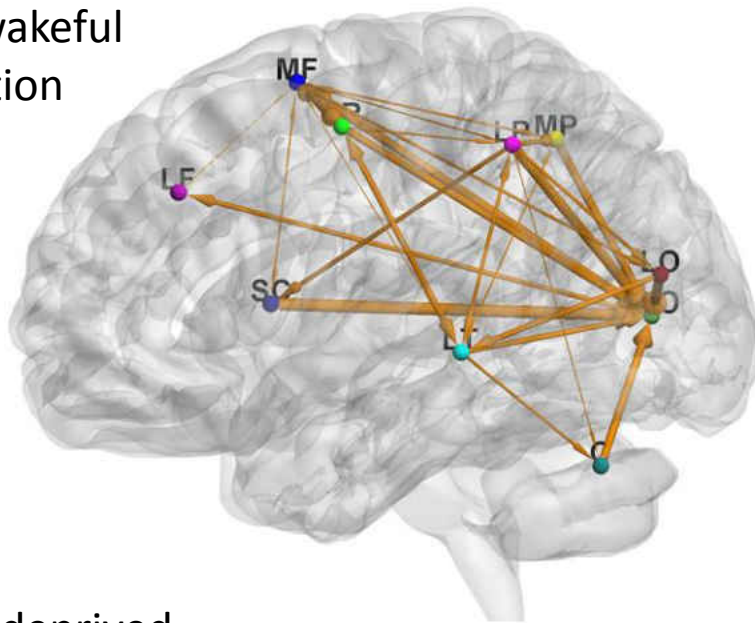Condition

Sleep-deprived
Condition

Figure 34 Subject 4: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

Rest-wakeful
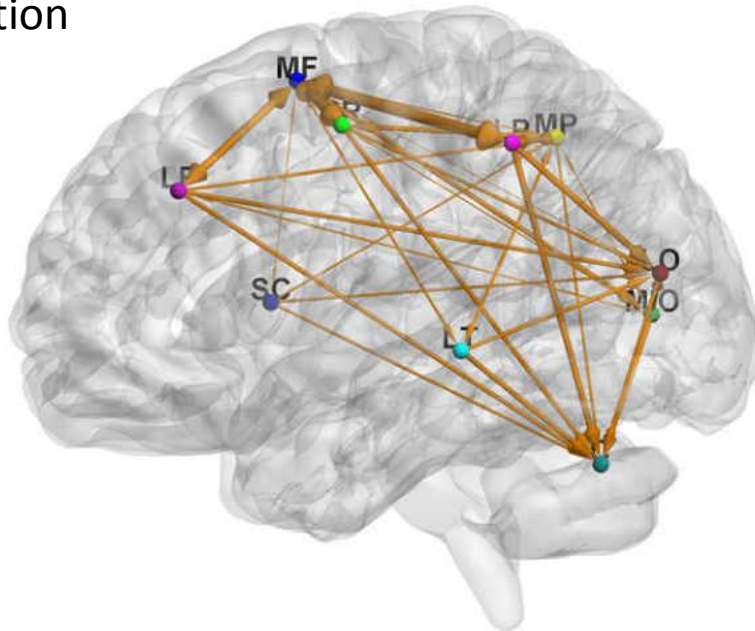Condition

Sleep-deprived
Condition

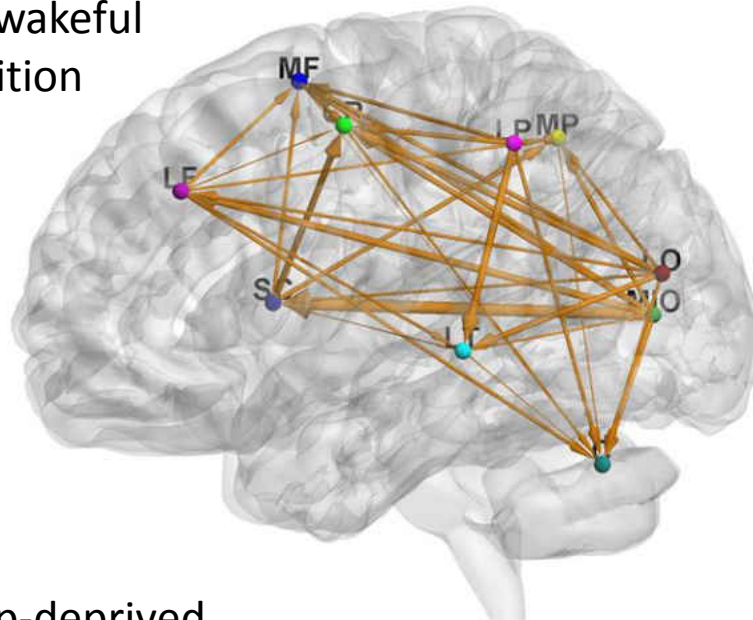Figure 35 Subject 5: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

101

Rest-wakeful Condition

Sleep-deprived Condition

Figure 36 Subject 6: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

Figure 37 Subject 7: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)
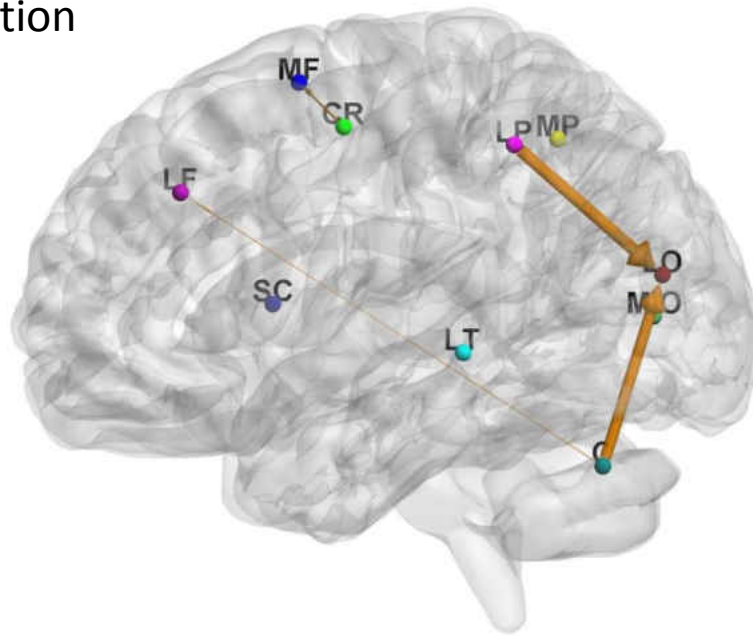
Figure 38 Subject 8: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)
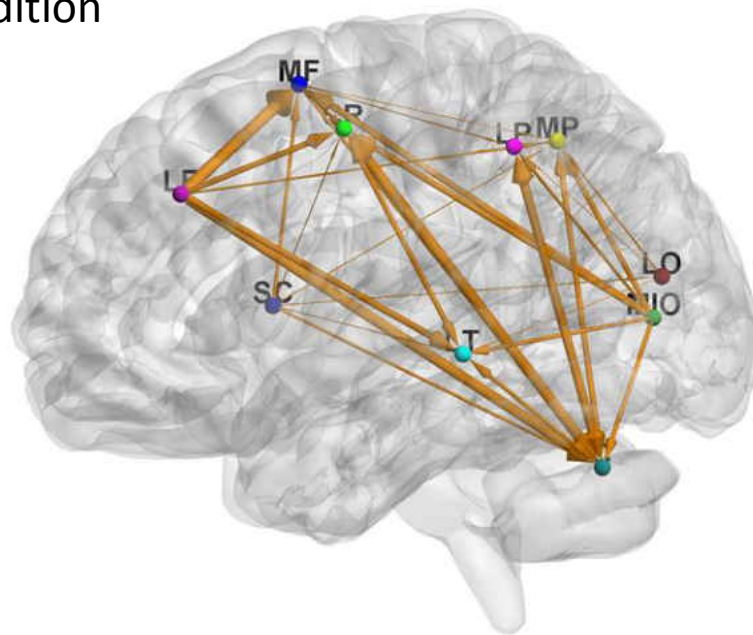
Rest-wakeful
Condition
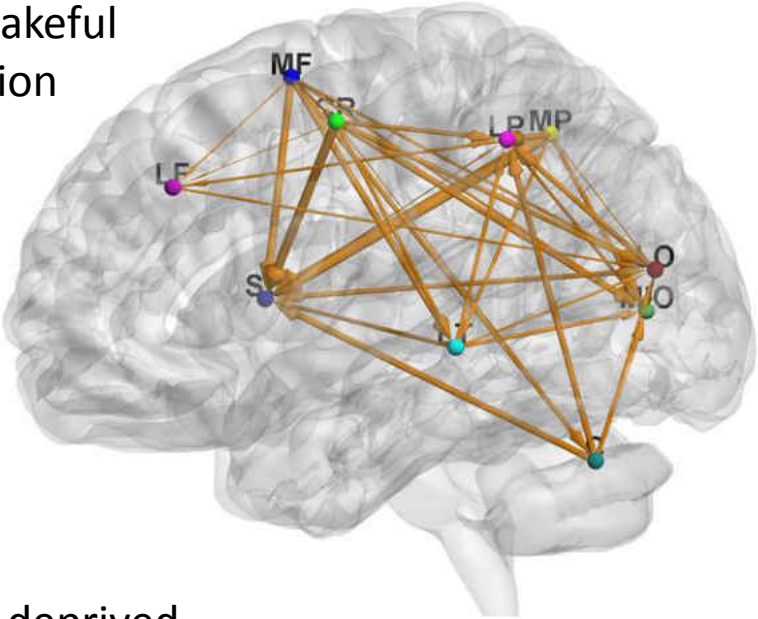
Sleep-deprived
Condition
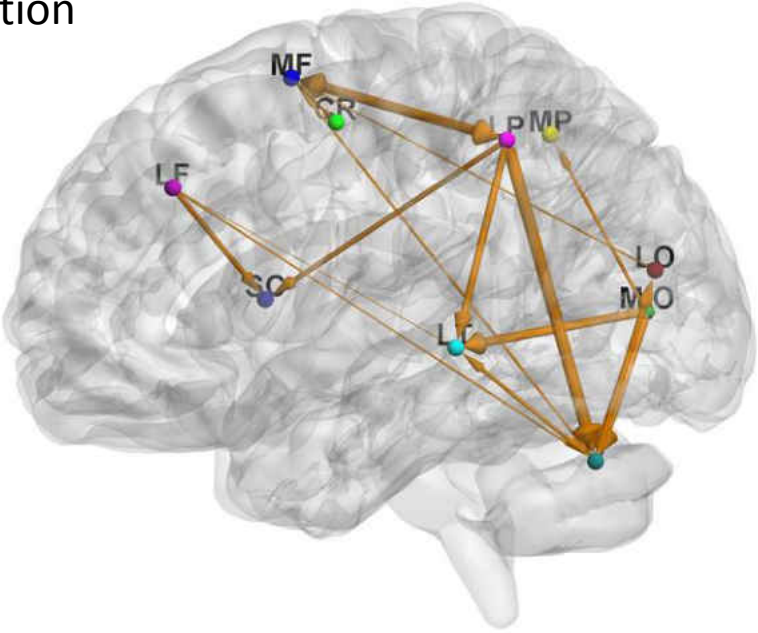
Figure 39 Subject 9: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

Rest-wakeful
Condition

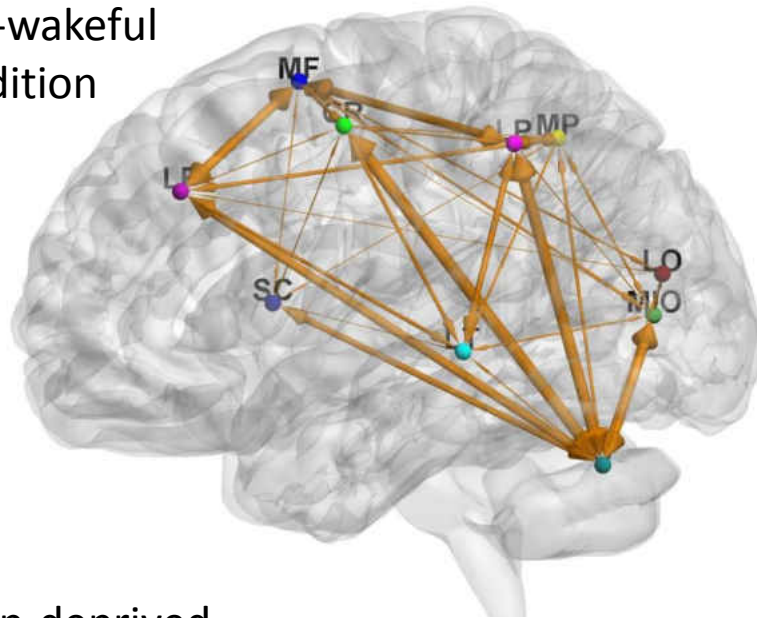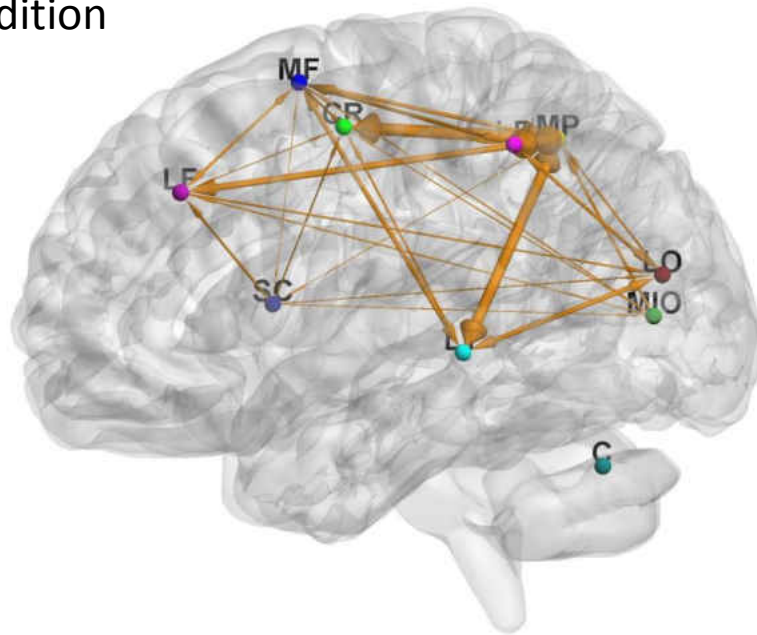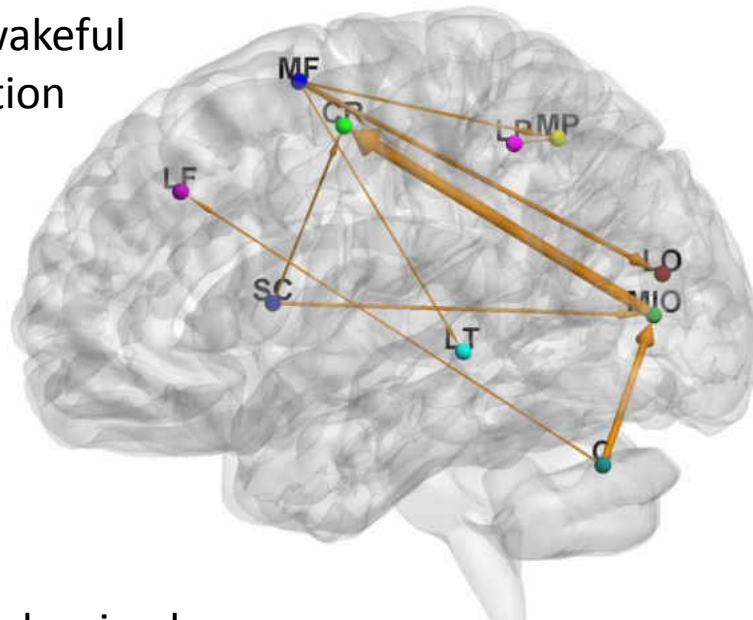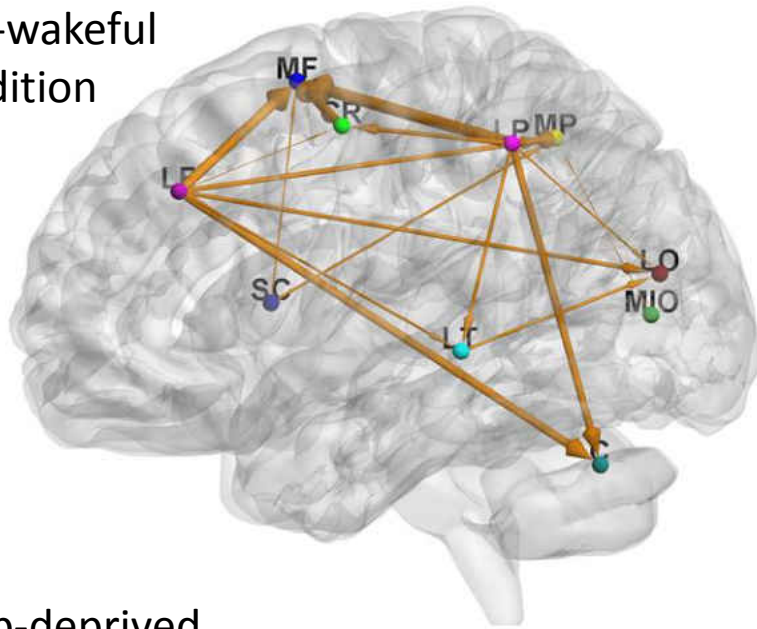Sleep-deprived
Condition
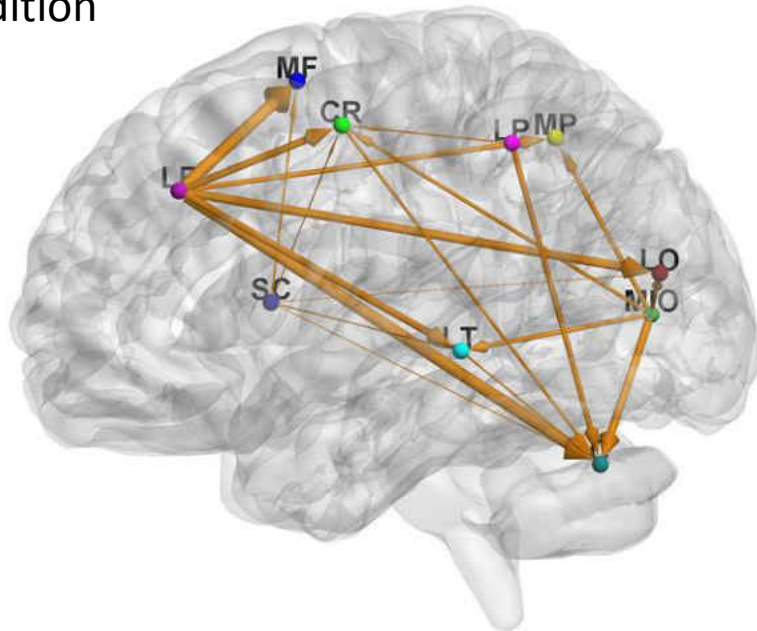
Figure 40 Subject 10: Model of Effective Connectivity
in the Rest-wakeful Condition (Top) and in the Sleep-deprived Condition (Bottom)

APPENDIX B:
SPEARMAN RANK CORRELATION BETWEEN RESIDUAL
GRANGER CAUSALITY AND RESIDUAL RESPONSE TIME
(ALL SUBJECTS)
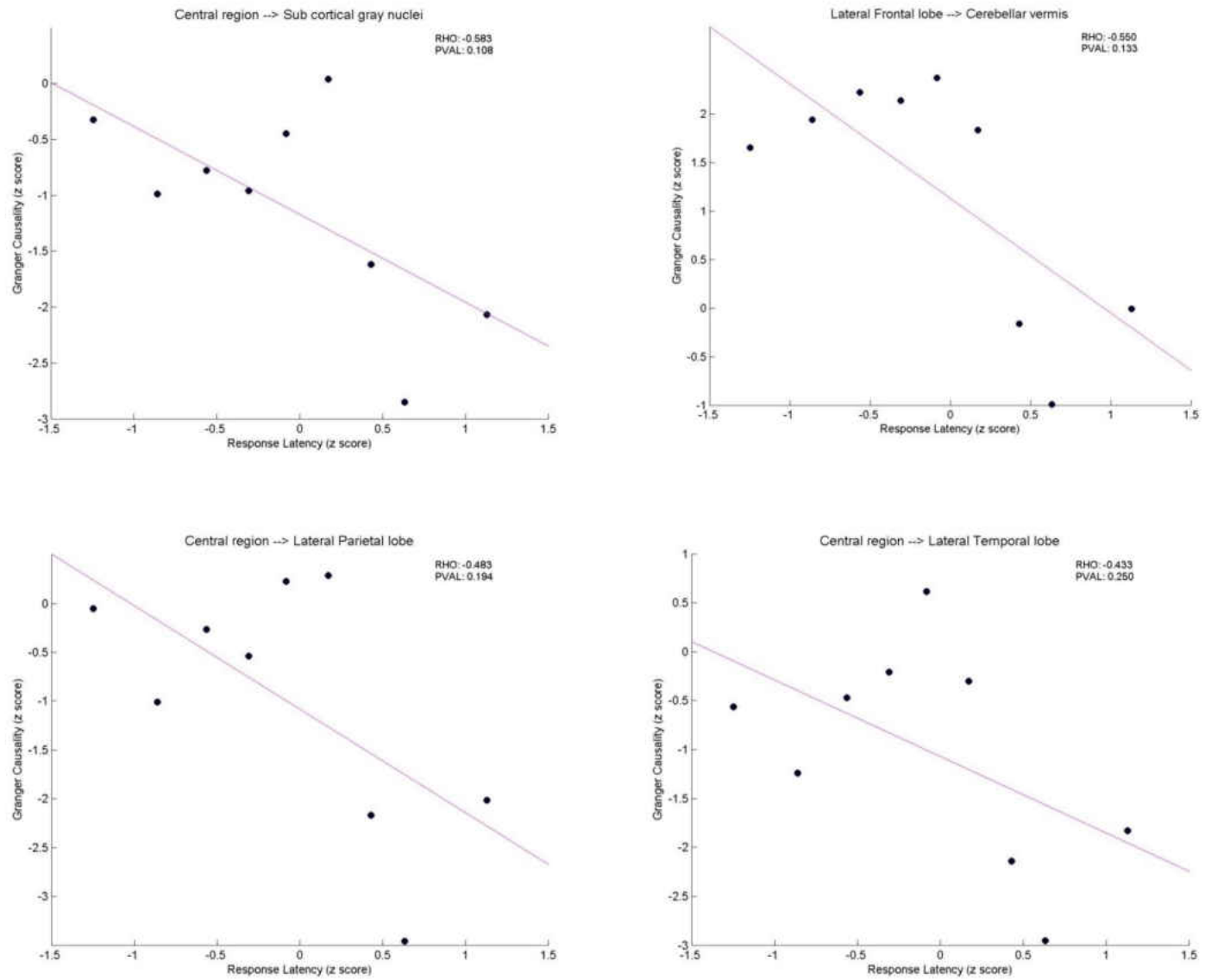
Figure 41 Spearman Rank Correlation between Residual Response Time and Residual Granger Causality

(CR→SC, CR→LT, CR→LP, LF→CB)
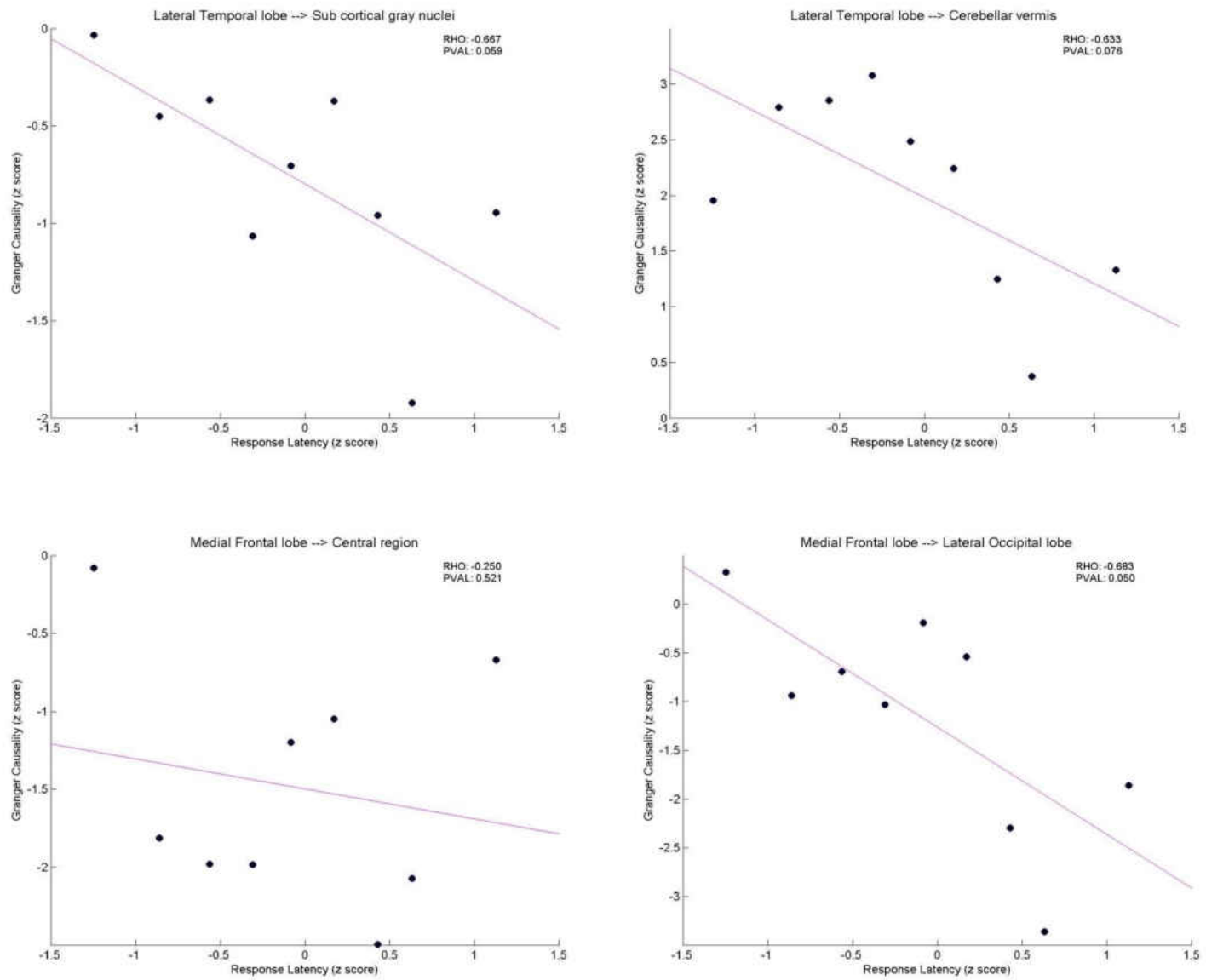
Figure 42 Spearman Rank Correlation between Residual Response Time and Residual Granger Causality
(LT→SC, LT→CB, MF→CR, MF→LO)
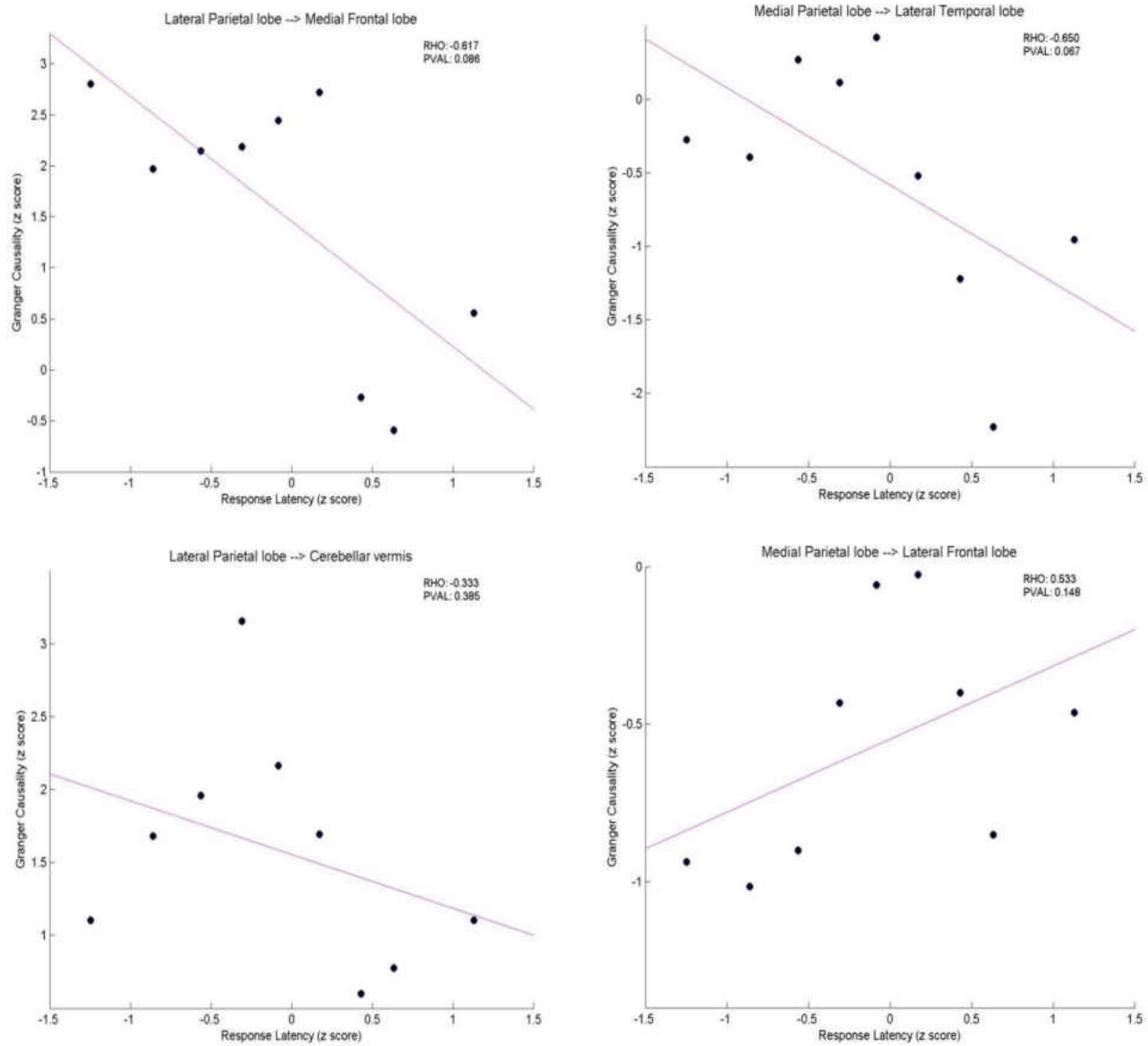
Figure 43 Spearman Rank Correlation between Residual Response Time and Residual Granger Causality
(LP→MF, LP→CB, MP→LF, MP→LT)
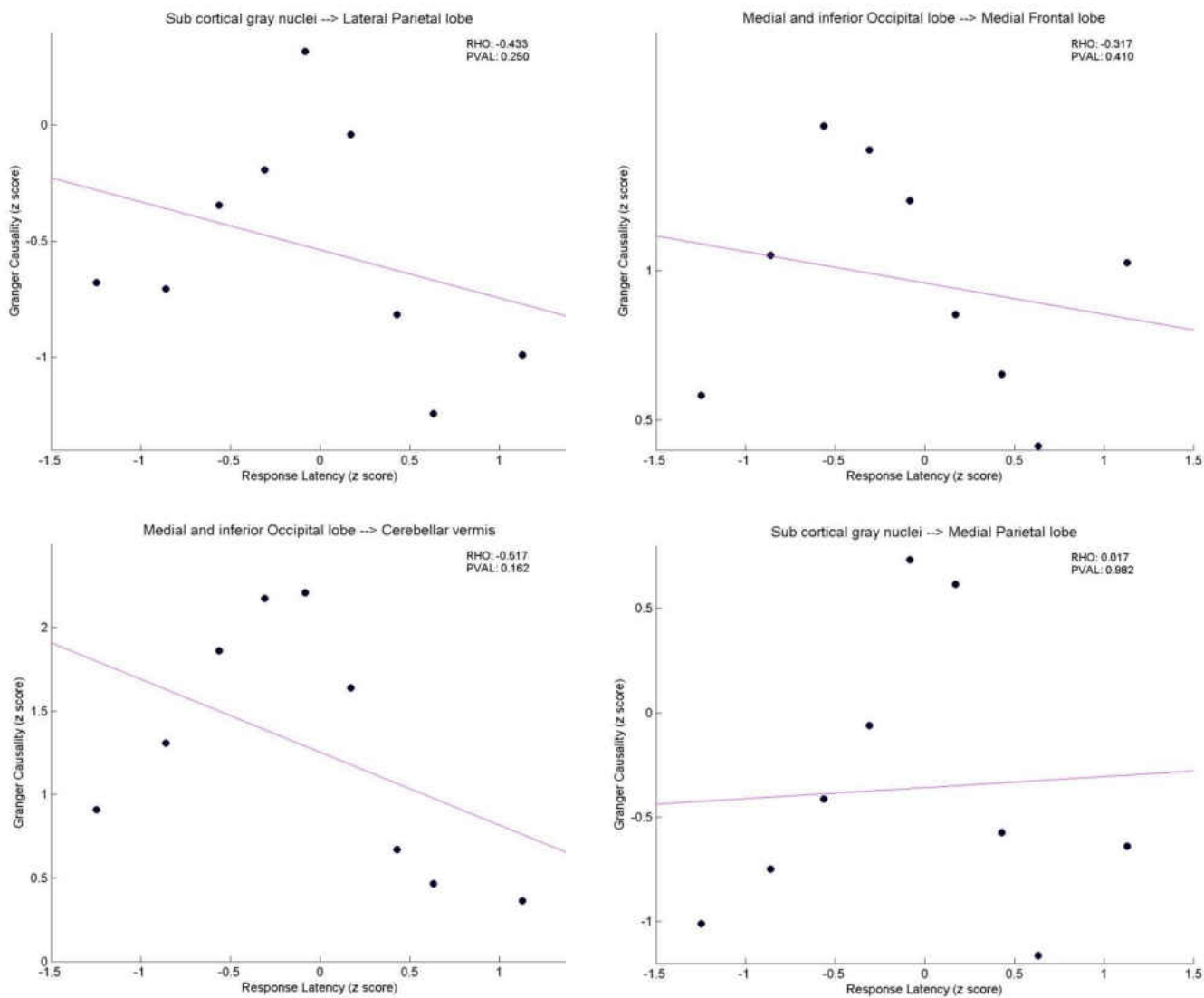
Figure 44 Spearman Rank Correlation between Residual Response Time and Residual Granger Causality
(MIO→MF,MIO→CB,SC→LP,SC→MP)

111
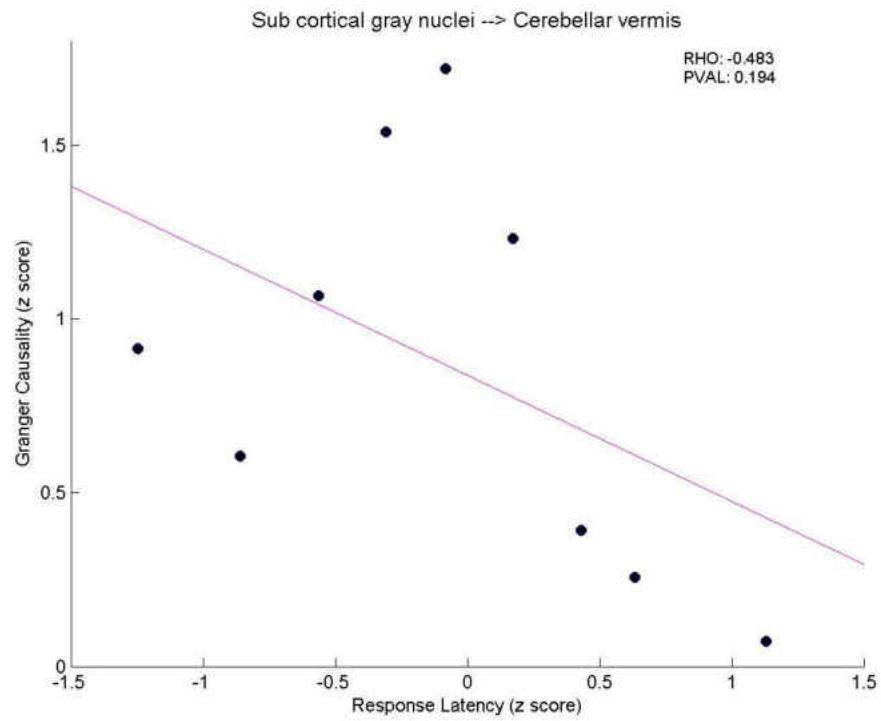
Figure 45 Spearman Rank Correlation between Residual Response Time and Residual Granger Causality
(SC→CB)

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