DEVELOPMENT OF NEUROPHYSIOLOGICAL APPROACHES FOR MONITORING AND INTERVENING MENTAL FATIGUE

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Declaration

I hereby declare that the work presented in this thesis is my own and it has been written by me in its entirety. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

This thesis has not been submitted for any degree in any university previously.

Bui Ha Duc

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Summary

The aim of this thesis was to develop neurophysiological approaches for monitoring and intervening mental fatigue. Along with the increase of demanding mental effort work, mental fatigue becomes a common phenomenon in modern daily life and has negative impacts on cognitive processing. Although many approaches have been developed to monitor mental fatigue, a neurophysiological indicator of mental fatigue is still needed to precisely assess and prevent it. To achieve the target, this study first utilized fMRI and EEG techniques to investigate the effects of mental fatigue on the brain activation and the functional connectivity between thalamus and other brain areas. The results showed that EEG spindles, as a result of physiological burst firing mode of thalamic reticular nucleus (TRN) in releasing GABA that block connectivity between the thalamus and cerebral cortex, vary with mental fatigue levels and spindles can indicate both circadian and work-induce mental fatigue.

Second, a novel EEG approach using spindle activity as the indicator was proposed to monitor mental fatigue and predict unintentional sleep onset. The proposed method is based on the biological mechanism of sleep instead of the classification methods used in the literature. The results showed a high correlation between the new approach and traditional visual behavior score ($r = 0.852$; $p<0.01$). Critically, the spindle-based approach seem to be more sensitive to the abruptly changes of drowsiness and can provide the level of fatigue at any given time since it directly reflect the alteration caused by mental fatigue in the brain, while visual behavior

can only observe the outcome of this process. Additionally, it can predict when the subjects have high possibility to experience microsleep long time ahead (from 3 to 15 minutes ahead).

In practical situations, it has been shown that fatigued people usually underestimate the likelihood of falling asleep and keep working even though they may aware of their level of fatigue at the time, leading to unexpected accidents. Hence, in the third study, trigeminal nerve stimulation was utilized to intervene and suppress the effects of mental fatigue. The results showed that trigeminal stimulation could quickly suppress the effects of mental fatigue (in less than 10s). This provided a promising non-invasive method for mental fatigue intervention.

In conclusion, this work provided an essential step toward the development of a system that can provide reliable and early feedback on individual's fatigue level at any given time and deliver stimulation to quickly suppress the fatigue effects. The system can essentially contribute to the prevention of fatigue related accidents, which has become more inevitably common nowadays.

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List of Abbreviations and Symbols

ACC	anterior cingulate cortex
AC-PC	anterior commissure-posterior commissure
BF	basal forebrain
BOLD	blood oxygenation level-dependent
CFS	chronic fatigue syndrome
ESS	Epworth Sleepiness Scale
ESPS	excitatory postsynaptic potentials
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GLM	general linear model
HR	hemodynamic response
IPL	inferior parietal lobe
ISPS	inhibitory postsynaptic potentials
LC	locus coeruleus
MFC	medial frontal cortex
MR	magnetic resonance
MS	multiple sclerosis
NA	Noradrenaline
ROI	region of interest
PET	positron emission tomography
PFC	prefrontal cortex

PPC	posterior parietal cortex
RT	reaction time
SCN	suprachiasmatic nucleus
SMA	supplementary motor area
TBI	traumatic brain injury
TC	thalamocortical connection
TRN	thalamic reticular nucleus

Chapter 1

Introduction

1.1 Motivation

Fatigue has been one of the core constructs for theory and research since the beginning of modern psychology. By the early 1900s, some studies of mental fatigue were conducted in Germany and United States of America. These studies focus on the question of prolonged work's effects on performance of tasks that involve cognitive functions of memory, judgment, reasoning and other typical components of intellectual abilities. The flow of research on mental or cognitive fatigue reached its peak in 1940s, when fatigue was an issue of high importance in military and industrial contexts, and in 1980s, when the new models and theories of cognitive processing were raised. Over the past 100 years, a considerable number of articles, reports on fatigue have appearing in the literature, providing the foundation for research in this domain. However, the underlying mechanism of mental fatigue has not been explained and its definition has not departed from the early assessments either.

Mental fatigue is usually considered as a phenomenon universally experienced at a phenomenological level. It refers to the feeling that people may experience after or during prolonged periods of demanding cognitive activity and is characterized by subjective feelings of “tiredness” or “lack of energy” (Boksem and Tops, 2008) . Along with the increase of demanding mental effort work, these feelings are prevalent in everyday modern life and there has also been a substantial increase in the number of applications related to fatigue. In particular, in the past few decades, military applications have remained a central concern for fatigue research and theory (Caldwell, 2005). In addition, civil occupations in aviation, healthcare, shift work, and other work settings have been the topic of recent research. A recent survey of the U.S. workforce (Ricci et al., 2007) showed that 38% of workers reported being fatigued. In the Netherlands, half of the women and a third of the men in the working population complain about being fatigued, while 15 years ago, only 38% of the women and 24% of the men reported such complaints. It is estimated that lost productivity time from fatigued workers cost employers an excess of a hundred billion dollars annually. Mental fatigue has also been identified as a major debilitating and even life-threatening factor in working populations (Dinges, 1995; Lal and Craig, 2001; Okada et al., 2004). According to National Sleep Foundation’s (NSF) 2012 report, one in five pilots (20%) admit that they have made a serious error and one in six train operators (18%) and truck drivers (14%) report that they have had a “near miss” due to fatigue. Moreover, cognitive fatigue is prevalent in a large number of chronic medical conditions such as cancer, Multiple Sclerosis, Chronic Fatigue Syndrome, Alzheimer's disease, and Parkinson's disease (Chaudhuri and Behan, 2000). Therefore, an accepted and sufficiently accurate assessment of fatigue is the first step towards achieving the further aims of predicting fatigue and increasing the available means of preventing it.

However, the key limitation of cognitive fatigue studies is the lack of a neurophysiological approach that can deal with the complex nature of mental fatigue. Although widely used, assessment of subjective fatigue generally involves a complex of other cognitions, such as dissatisfaction with performance, decreasing interest or motivation, intrusions of off-task thoughts, which can be biased and affect the accuracy. In contrast to subjective assessment, direct measurement of performance is more objective and can be verifiable by outside observers. However, the dissociation between subjective fatigue and performance decrease suggests that both approaches might not be adequate to reflect what is happening in the brain during mental fatigue. In recent years, functional neuroimaging has been used infrequently to examine relationships between brain responses and cognitively challenging tasks. Though much remains to be learned, functional neuroimaging appears to hold the potential of enriching our understanding and improving the measurement of fatigue. Furthermore, less attention has been paid to develop a fatigue intervention method. Some studies have been reported that exposure to blue-enriched white light during daytime work-hours could improves subjective alertness, performance, and evening fatigue (Vandewalle et al., 2009; Viola et al., 2008). However, this technique requires long exposure time to start working, making it less acceptable in real life situation. These gaps set the motivation for the present study.

1.2 Research objectives

The aims of the present study were to develop novel neurophysiological approaches for monitoring and intervening mental fatigue. The sequences of objectives to accomplish these aims were:

- Investigate the effect of mental fatigue on brain activation and brain connectivity. From there, determine the neurophysiological indicator of mental fatigue.
- Utilize this neurophysiological indicator in detecting and predicting mental fatigue.
- Develop an approach for fatigue intervention which can mediate the fatigue level in a short time.

In order to achieve these objectives, this study is separated into three smaller studies. The first study was to determine the brain regions susceptible to cognitive fatigue as well as the influences of mental fatigue on the functional connectivity between these susceptible regions and other areas since mental fatigue may not only impair regional activation but also the integration of regional brain activity.

Secondly, a novel EEG approach was proposed to monitor fatigue based on the findings from the first study. This approach used EEG spindles, result of physiological burst firing mode of TRN in releasing GABA that block connectivity between the thalamus and cerebral cortex, as a neurophysiological indicator for mental fatigue.

And finally, trigeminal nerve stimulation (TNS) was utilized to intervene and suppress the effects of mental fatigue in this study. The advantage of trigeminal nerve stimulation is that it is a non-invasive technique to modulate the activity of targeted brain regions by sending mild electrical signals through branches of the trigeminal nerve.

This research sought to make contributions toward the development of a practical system that can provide accurate and early feedbacks on individual's fatigue level and mediate the negative effects of mental fatigue. Therefore, more attention has been paid to non-invasive and potentially portable techniques such as EEG and TNS than other approaches. The findings of the study could serve to build tools of detecting and intervening fatigue. The study also serves to make inputs to the existing knowledge on the mechanism of mental fatigue.

1.3 Thesis Organization

This thesis contains seven chapters:

- Chapter 1 presents a brief introduction to the topic and outlines the research objectives of this study.
- Chapter 2 extensively reviewed published literature on mental fatigue and the approaches to access mental fatigue. This chapter also surveyed the role of thalamus in regulating mental states.
- Chapter 3 details the general experimental materials and methods used in this study. In next three chapters, the results obtained by experiments will be presented and discussed.
- Chapter 4 discusses on the neural correlates of mental fatigue and the

effects mental fatigue on thalamo-cortical functional connectivity. Based on the findings, the association of EEG spindles to mental fatigue was showed and discussed.

- Chapter 5 describes the application of the knowledge obtained from chapter 4 in monitoring and predicting mental fatigue.
- Chapter 6 presents a novel approach for fatigue intervention.
- Chapter 7 summaries the major findings of the research and suggests several recommendations for future work.

Chapter 2

Literature Review

Being one of the most common phenomena and having significant impacts on human daily life, cognitive fatigue has been gaining widespread attention since the 1890s. Over 100 years, many researchers have spent their whole life to clarify the meaning and measurement of mental fatigue. Although the underlying mechanism remains unclear, previous studies have laid the foundations and the motivations for research in this domain. In this chapter, a brief historical background of mental fatigue will be presented, along with its assessment and measurement. This chapter also reviews the recent uses of neuroimaging in studying fatigue, which forms the motivation of this study and the role of thalamus in regulating mental states.

2.1 Historical background

Mental fatigue or a decrement in performance from excess mental effort gained widespread attention in the 1880s. In the early twentieth century, researchers were mainly interested in the effects of prolonged work on performance of tasks as well as the experience and physiology of fatigue as these affected workers' productivity. To this end, Harvard University's Graduate School of Business set up a Fatigue Laboratory in 1927, where investigators continued research into various aspects of fatigue until 1947. Because worker fatigue impaired performance, a scientific and systematic study of fatigue was encouraged. Henderson, one of the laboratory's founders, noted that "business leaders, engineers, physiologists, and the general public" all agreed fatigue was important, but found no agreement on its definition.

Some early researchers (Ebbinghaus, 1896) were mainly interested in the effects of prolonged work on performance of task that involved cognitive functions of memory, judgment, reasoning, and other typical components of intellectual abilities. However, other researchers (Muscio, 1921a, b) were concerned with the subjective aspects of mental fatigue, which involve a panoply of different motivational and attitudinal factors. Some researchers (Bartley and Chute, 1947; Floyd and Lewis, 1954) limited use of the term fatigue to subjective fatigue, whereas others (Dodge, 1913, 1917) termed performance effects associated with fatiguing conditions as work decrement.

Since the 1980s, there has been a surge of new theoretical interest in fatigue, with the rise of new models and theories of cognitive processing, attention, and motivation and the availability of new behavioral, physiological, and neuropsychological strategies and tools for empirical inquiry. As a result, in the past 4 decades, there has been nearly a ten-fold increase in the number of articles, chapters, and reports on fatigue that have appeared in the psychological literature.

Fatigue researchers have adopted these new techniques to attempt to understand the task characteristics and person characteristics that lead to fatigue, both in laboratory and in the field, through experience sampling and other longitudinal procedures. Other approaches to fatigue have involved attempts to develop theoretical or mathematical models of the operators' task behavior over extended periods of time or during periods of sleep deprivation. In addition, measurement of neural activity, through event-related potentials or functional magnetic resonance imaging, has started to produce results that help pinpoint the locus of mental fatigue effects. Challenges still exits to link up the effects of mental fatigue to neurological processes and to other cognitive processes and behaviors. However, recent research efforts are providing the foundation for future research in this domain.

2.2 Definition of mental fatigue

2.2.1 Conceptual issues for mental fatigue

The quest to clarify the meaning of mental fatigue has challenged researchers and clinicians for many years. Despite the common use in casual conversation and scientific report, the term "fatigue" has defied efforts to provide a single, broadly acceptable definition. Instead, its meaning tend to vary with the circumstances in which it is used. Mental fatigue is sometimes defined as subjective feeling such as "tiredness", feeling tired, being fatigued, feeling weak in part of the body, tired or lacking in energy, or experiencing "everything an effort" (Cope, 1992). Fatigue has been referred to the feeling that people may experience after or during prolonged periods of cognitive activity. However, fatigue may also be experienced after working for a relatively short period of time, while working long hours does not always lead to fatigue. Some studies relate mental fatigue to the individual decrements performance, but the lack of correlation between performance deficits and subjective reports has complicated the understanding of fatigue. The troubles in defining mental fatigue come from its complex nature, which has been shown to involve a numerous of psychosocial and behavioral processes.

2.2.2 Task characteristic and mental fatigue

Numerous of tasks have been investigated for the effects of fatigue in the context of both performance effects and subjective fatigue. In general, the characteristics that are well-known to lead to increased mental effort, impaired learning and stress are also the most salient for the investigations of cognitive fatigue.

The most prominent variable associated with studies of fatigue is the sheer amount of time on task. Studies of performance effects on fatigue have ranged from periods of a few minutes in duration (Gates, 1916) to several weeks of 8 hour/day continuous mental multiplication (Arai, 1912; Huxtable et al., 1945). It is estimated that in cognitive tasks of duration up to 2 hours, the maximum degree of impairment was about 10% in performance level. Many studies of fatigue however show minimal performance decrements in mean performance over periods up to a few hours of continuous time on task.

Mental fatigue performance effects are typical associated more with tasks that require high levels of effort than tasks that require low levels of effort. As Bartley and Chute (Bartley and Chute, 1947) noted, when task have low levels of cognitive demands, the operative mental state is one of boredom rather than fatigue. However, Cameron (Cameron, 1973) suggested there is a relationship between the level of attention effort demanded by the task and the speed with which fatigue develops. More demanding tasks over a short period of time may results in and amount of fatigue that is similar to that proceeded by a less demanding task carried out for a longer period.

Another category of task characteristic that has been repeatedly implicated in mental fatigue study is the motivation factors. The most prominent motivation factor related to mental fatigue is whether or not the task is interesting or enjoyable to individual performing it. A frequent concern of early theorists and researchers in this domain of mental fatigue is the distinction between performing a task that is intrinsically interesting or personally enjoyable and one that is not interesting or enjoyable. Some authors (Broadbent, 1953), have noted significant overlap among the fundamental cognitive processes involved in work and leisure activities, for example reading a book for pleasure or reading a section of text in the context of an ability or achievement test. In fact several studies have noted that one of the key characteristics of fatiguing situations is that they involve tasks that the individual would just as soon not be doing. Dodge (Dodge, 1913) noted that there did not appear to be any more energy required in play than in work but that the essence of work is that it can be accomplished only again resistance.

2.2.3 State variables and mental fatigue

Several state variables have been identified as significant influences on mental fatigue. The most extensive research in this area has focused on long term cognitive fatigue like over 12 hours or more time on task or over a period of several days or weeks in the context of military or occupational work schedule studies (Miller et al., 2008). However, even for a short-term (less than 6 hours) studies, there is a growing body of evidence concerning the effects of these sate variables on the onset of mental fatigue. Most of these state variables relate in one way or another to the individual’s arousal level while performing the task.

Many studies have focused on the effects of sleep deprivation o task performance. It should be noted that this is not task-induced fatigue but rather fatigue induced prior to task engagement. Sleep deprivation study results have provided mixed results (Drummond and McKenna, 2009) but generally show that a complete lack of sleep on the night prior to extended time on task results in lower levels of performance and more rapid onset of cognitive fatigue. Short naps after extended time on task have been found to partially reduce fatigue effects, which is consistent with the conceptualization of sleep as restorative for baseline arousal levels.

Studies on time-of-day effects and mental fatigue also indicate that as far as mean performance is concern, resistance to fatigue is higher during morning task sessions than it is in the afternoon or evening (Gates, 1916). However, Revelle and his colleagues (Revelle et al., 1980) have shown that time-of-day effects could covary with individual differences in personality traits. If an individual is at a trough in his or her normal circadian rhythm, it can be expected that fatigue effects may be exacerbated.

2.2.4 Theories of mental fatigue

There have been several attempts to provide a generic theoretical framework for understanding the nature of mental fatigue effects as presented below. Each of these theories describes important, partially overlapping, yet partially unique, determinants and characteristics that relate to fatigue. Together, they identify a set of factors that must be considered in any overarching theory or model that can be expected to predict the task, situation and person characteristics that result in mental fatigue, the time course of fatigue and the potential for remediation of performance effects associated with fatigue.

Grandjean theory

Grandjean (Grandjean, 1968) proposed a general approach to conceptualization fatigue. In his view, fatigue could be compared to the level of liquid in a container. Many different sources fill the container the day over and lead gradually to the sensation and the state of fatigue. In everyday experience fatigue is an accumulation of the effects of the various sources. Recovery is shown as the outflow from the container. The processes of recovery primarily take place during sleep, and to some extent also during every rest pause and leisure time. Environmental influences, internal physical influences and task characteristics combine to contribute to a general accumulation of fatigue in individual, which is alleviated by time allocated off task or out of the situation.

Kahneman theory

Kahneman's model (Kahneman, 1973) is not a dedicated model of mental fatigue but a broad model of attention. However, the components of this model include constructs that are critical to the development and expression of fatigue-related performance changes. First, this model indicated that an individual's overall level of arousal which is determined by enduring dispositions (e.g. task interest) and momentary intention (e.g. task motivation), results in the distribution of attentional resources to the criterion task and away from the criterion task. A feedback loop determines whether the goals are being met and whether it is necessary to either increase or decrease arousal level or change the allocation of policy of the activities to which attention is directed. Using Kahneman's model, one can represent aspects of the fatiguing task situation in terms of available attentional capacity, level of arousal, and the discrepancies between amount of attention allocated to the task and the task demands on attention.

Hockey theory

Hockey's model (Hockey, 1993) draws on elements of Kahneman's model of attention, but includes specific representations of task goals, an executive controller, and a feedback loop. As noted by Hockey (Hockey, 1997; Hockey and Earle, 2006), effort allocations in this model do not increase automatically as a function of discrepancy between performance levels and task goals. Instead, the individual evaluates discrepancies in the context of a "budget" for effort expenditure. The maximum effort expenditure is partly related to motivation influences and partly determined by "individual differences in the perceived value of tasks goals, in response to the challenge, in the capacity for sustained work, and in the tolerance of aversive states associated with high levels of strain". When the demands for effort exceed effort budgeted for the task, there may be a downward revision of task goals to minimize the overall discrepancy. Ultimately, the individual may completely disengage from the task when the discrepancy between effort demanded and effort budgeted is too large. The Hockey's model was later detailed by Boksem and Top (Boksem and Tops, 2008) through the pathway of dopamine influx into the prefrontal cortex. They proposed the changes of dopamine influx alter the ongoing behavior in a way to promote energy conservation or change the focus of attention to more rewarding behaviors.

Kanfer and Ackerman model

The integrated resource allocation model proposed by Kanfer and Ackerman (Kanfer and Ackerman, 1989) extends Kahneman's general model of attention and effort to address the role of individual differences and motivational processes in the context of task performance over time. In particular, Kanfer and Ackerman's model proposes that the quantity of resources available for the allocation is a joint function of ability and the individual's intended level of attentional effort. In addition, attention allocation policy is described in terms of the pattern of distribution across three areas: task effort, off-task thoughts and distractions, and attention related to self-regulation.

Additional properties of Kanfer and Ackerman's model also have relevance to the issue of fatigue effects on performance. Off-task thoughts (e.g. anxiety, performance evaluation apprehension) will also draw attention away from the task. The processes of self-regulation activities also appear to be attentional resource consumptive. If self-regulation is directed toward control of emotional reactions, then there may be a decrease in resources available for the task because self-regulation processes also consume resources.

2.3 Assessment and measurement of mental fatigue

Researchers have taken many different approaches to the definition of mental fatigue over the past 100 or so years. Broadly, fatigue can be assessed based on subjective feeling or performance decrement (Wessely et al., 1998).

2.3.1 Subjective assessment

Subjective patient reporting was considered as the primary approach to measuring fatigue today. A remarkable number of fatigue questionnaires have been developed over the years (e.g. Fatigue severity scale (FSS), Fatigue assessment instrument (FAI), Fatigue impact scale (FIS), Profile of mood states (POMS)). Scales have been developed for use in a variety of clinical populations, including cancer, chronic fatigue syndrome, myasthenia gravis as well as for healthy individuals engaged in work and sports. Self-report measures are uniquely able to assess the feelings associated with fatigue, but can only indirectly assess changes in performance from the respondent’s perspective.

Most scales, particularly the multidimensional ones, include items to assess both the feelings of fatigue and the perceived impact of fatigue on the lives of respondents. The subjective feelings measured include not only the core feelings of fatigue (e.g., tiredness), but also motivational (e.g., reduced motivation) and affective (e.g., negative affective feelings) feelings accompanying fatigue. To assess the impact of fatigue, some scales ask about the degree of interference with daily activities (e.g., occupational activities). Scales commonly distinguish between the impact of fatigue on mental/cognitive (e.g., impaired concentration) and physical/muscular (e.g., reduction in sustained physical activity) activities. It is important to note that, though subjective feelings and fatigue impact are separate categories of items, both types of items are measured on the basis of the subject's self-report rather than direct performance assessment.

Fatigue questionnaires have a number of practical advantages over direct measures of performance. They are inexpensive, readily available, and quickly administered. They require little staff training, and place few demands on seriously ill patients.

Despite the emphasis on self-report in measuring mental fatigue, these measures have been known for at least a century to correlate poorly with cognitive dysfunction. Self-report measures are subject to influence by a variety of factors, including mood and recall biases, which can reduce their accuracy. For instance, the level of subjective fatigue in MS is not related to a decline in working memory (DeLuca et al., 1995), short term memory (Johnson et al., 1998), executive function or complex attention (Cummings, 1995; Krupp and Elkins, 2000), vigilance (Paul RH et al., 1998), verbal fluency (Rao et al., 1991), or verbal memory (Paul RH et al., 1998).

2.3.2 Relationship between Subjective Perceptions of Fatigue and Performance Decrements

Aside from questionnaires, the other major approach to assessing fatigue is the direct measurement of performance decrement. Healthy persons with induced fatigue (e.g., through performance of cognitively demanding task) have been shown to display cognitive declines in planning ability and increases in perseverative errors compared to non-fatigued individuals (van der Linden et al., 2003). Healthy persons have also displayed shifts toward lower-effort, higher-risk responses after being fatigued by a simulated workday of mentally demanding tasks (Schellekens et al., 2000). Others researchers who examined the real-world consequences of long work hours found an increase in operator errors among employees working a 12-hour shift in nuclear power plants (Baker et al., 1994). The important advantage of performance-based measures is that they provide data that is objectively verifiable by outside observers. However, the lack of correlation between objective measurement and subjective experience that hinders better understanding of the enigma of fatigue.

Most of objective studies examined cognitive performance over the course of an experimental induction of mental fatigue using two general approaches. First, mental fatigue can be conceptualized as decreased performance over a prolonged period of time, such as during the course of a work day. Hence, at the end of a long day people often complain “tired”, “do not want to think”. A second approach to cognitive fatigue could be viewed as decreased performance during acute but sustained mental effort or time awake. This conception of fatigue is similar to that typically seen in the motor fatigue literature, in which fatigue is defined as a failure to maintain a required force or output of power during sustained or repeated muscle contraction.

A 3-hour neuropsychological testing session was used by Johnson and coworkers (Johnson et al., 1997) to induce fatigue in persons with multiple sclerosis (MS), chronic fatigue syndrome (CFS), and clinical depression, and in healthy control subjects. Subjects were asked to rated their subjective fatigue during the testing session and completed the Paced Auditory Serial Addition Test (PASAT) (Brittain et al., 1991) immediately after each rating to relate subjective ratings of fatigue with objective neuropsychological performance. The hypothesis was that the induced fatigue with prolonged mental activity would result in diminished cognitive performance in the three fatiguing clinical groups relative to controls. However, despite increased levels of subjective fatigue over the 3-hour session, all groups showed the same increase in PASAT performance over time, likely a result of practice effect. There was no relationship between subjective fatigue and PASAT performance.

Another study conducted by Riese and associates (Riese, 1999) examined mental fatigue in persons with severe Traumatic brain injury (TBI) on a driving simulator. TBI and healthy control subjects were required to perform several sustained driving-related tasks at either 50 or 80 percent of each individual’s maximal performance level, which was established during a separate training session. Pre-test and post-test tasks of cognitive performance, subjective distress, and cardiovascular measures (heart rate and blood pressure) were obtained. No performance difference on behavioral indicators between the TBI and healthy control groups was showed in the result. However, TBI subjects may pay “higher physiological costs” for sustained performance on the dual-task paradigm.

Lim and colleagues (Lim et al., 2009) showed that there was positive relationship between time-on-task and mental fatigue level in health control subjects, and no significant correlation between objective performance decline and either increases in self-rated fatigue was found.

Other studies conducted by Schinkel (Jennekens-Schinkel et al., 1988), Bruno (Bruno et al., 1993), Paul (Paul et al., 1998) showed consistent results. Taken together, prolonged cognitive effort produced an increase in the subjective experience of fatigue, but this increase did not translate into observable cognitive performance deficits.

A sustained working memory task was utilized by Krupp and Elkins (Krupp and Elkins, 2000) to demonstrate diminished performance over the course of time awake. The results showed that performances of MS and control subjects did not differ during the first half of an alpha-arithmetic test. However, relative to the first half of the alpha-arithmetic task (the A-A Test), MS subjects showed significantly slowed reaction time during the second half of the test than healthy control subjects.

Bryant (Bryant et al., 2004) examined fatigue in 56 persons with MS and 39 healthy controls matched for age and educational level. MS subjects were further subdivided into those with cognitive impairment (n=27) and those not cognitively impaired (n=29). Their results showed that MS subjects, whether or not they demonstrate cognitive impairment, were reaching the limit of their ability to sustain central executive load at an earlier point in PASAT administration than HC subjects.

In summary, sustained mental effort may cause decrease in cognitive performance, and subjective fatigue may not be reliably correlated with objective measures of cognitive fatigue.

2.4 Neural imaging findings of mental fatigue

In recent years, functional imaging has been used infrequently to examine relationships between objective brain image data and subjective reports of fatigue. Although most of studies examined the functional cerebral activity associated with cognitive functioning in clinical samples such as persons with TBI, MS, and CFS, acute mental fatigue caused sleep deprivation or driving task has been paid more attention recently. These studies suggest that the perception of mental fatigue may be a result of the alteration cerebral effort required to perform the same amount of cognitive work.

2.4.1 Neural correlates of mental fatigue

Mental fatigue in clinical populations has probably received the most attention in neuroimaging studies among fatigue studies. Christodoulou and coworkers (Christodoulou et al., 2001; Eichenbaum, 2010) examined patterns of brain activation in nine persons with moderate to severe TBI and seven healthy controls performing a complex working memory task during fMRI acquisition. Healthy control subjects showed cerebral activation primarily in the left hemisphere of the brain, involving the frontal and temporal lobes, as well as bilateral parietal lobe activation. In contrast, TBI subjects displayed bilateral activation that was more lateralized, primarily to homologous regions of the right hemisphere relative to controls. In addition, TBI subjects showed a pattern of more dispersed activation within both the ipsilateral (left) and contralateral hemispheres. It is suggested that the increased right hemisphere recruitment resulted from the TBI subjects' need for more cognitive effort than healthy controls because of damage to the underlying neural substrate that maintains and manipulates information in working memory. However, the TBI group performed more poorly on the behavioral task than healthy controls. Thus, the group differences in cerebral activation could be a result of actual task difficulty rather than perceived effort.

In another study, McAllister and associates (McAllister et al., 1999) examined working memory in persons with mild TBI during fMRI. Like the Christodoulou and coworkers (Christodoulou et al., 2001) study, these studies showed increased activation in the right cerebral hemisphere in regions homologous to left hemisphere activation observed in healthy controls. However, this activation pattern occurred in the absence of performance differences between the mild TBI and healthy control groups during the working memory task. Several recent functional imaging studies in persons with MS (Chiaravalloti et al., 2005; Staffen et al., 2002) and CFS (Cook et al., 2007; Lange et al., 2005) have reported similar results.

Beside clinical populations, the effects of mental fatigue on healthy individual have been also studied, especially in sleep deprivation and driving due to the ubiquity of these problems in modern daily life as well as the ease to conduct the experiment and to collect the data. The reports could be categorized by type of cognitive tasks.

Attention tasks

There are many types of attention (e.g., sustained, selective, spatial, and divided), but functional neuroimaging studies have mainly examined sustained attention and short-term visual attention. Sustained attention is the ability to focus on a single task for an extended period of time. Visual attention refers to the need to process a short stream of visual stimuli and respond to a specific target. In healthy individuals, sustained attention relies on the right middle frontal gyrus and inferior parietal lobe and, to a lesser extent, on the left inferior parietal lobe and bilateral thalamus. Shorter-term visual attention tasks rely more heavily on the extrastriate cortex, as well as the fusiform, lingual, and superior parietal regions, depending on the specific target of attention.

Studies using neuroimaging to examine mental fatigue induced by total sleep deprivation showed decreased whole-brain metabolism of glucose following sleep deprivation along with a decrease in alertness. In addition, the frontal and temporal lobes showed a decrease in absolute metabolic rates, whereas the parietal lobes showed an increase and the occipital lobes showed no change (Chee et al., 2008; Drummond et al., 2000). Besides, alterations were also seen in the thalamus, basal ganglia, and cerebellum.

Other studies used a finer temporal scale (around 10 to 20 minutes) to examine performance on the psychomotor vigilance task (PVT) (Adrienne M. Tucker, 2009; Van Dongen and Dinges, 2005), which measures sustained attention and arousal lability. In this task, an individual was requested to presses a button as soon as a millisecond counter starts, which begins randomly within a predetermined interval. The task requires sustained attention. Findings showed that the frontoparietal sustained attention network supported fast reaction times whether the subjects were alert or fatigued. These brain regions did not respond during slow reaction times under control conditions, but showed increased responses immediately following slow reaction times under mental fatigue. This was thought to reflect individuals reengaging in the task following a slow response because they received feedback regarding this slow reaction time. In essence, then, a slow reaction time prompts compensatory effort from an individual, and this compensatory response is captured in fMRI as an increase in activation in the frontoparietal sustained attention network following the slowest reaction times.

Driving fatigue studies found that the number of crashes was negatively correlated with activity in the posterior cingulate (Horikawa et al., 2005), while others observed that the ability to maintain a safe driving distance was negatively correlated with activity in anterior cingulate (Uchiyama et al., 2003).

Overall, it appears that fatigue results in decreased brain responses in regions underlying sustained attention demands, as well as diminished performance on sustained attention tasks. Nonetheless, it appears that fatigued individuals can indeed engage these attention regions for brief periods, but only when accompanied by compensatory activation within the thalamus. This brief engagement allows for intermittent normal levels of performance, despite the fact that average performance across the entire task is diminished with fatigue.

Working memory tasks

Working memory has long been a popular cognitive domain in fatigue research. This is because working memory tasks typically rely on brain function within the prefrontal cortex; the prefrontal cortex has traditionally been thought of as the brain region most vulnerable to mental fatigue; and electroencephalography (EEG) studies have consistently demonstrated that changes in the frontal lobes following fatigue contribute to cognitive performance deficits. The term ‘working memory’ refers to a large number of cognitive functions, however. It is likely that the specific aspect of working memory examined in any given study influences the measured effect of mental fatigue on brain function. The types of working memory tasks used in functional neuroimaging studies of fatigue include those requiring arithmetic, maintenance of information, and manipulation of information.

Arithmetic working memory relies on activation within the bilateral dorsolateral prefrontal cortex, anterior cingulate gyrus, and bilateral parietal lobes. Studies examined arithmetic working memory following mental fatigue showed inconsistent results. Some studies showed activation was confounded by the sustained attention demands of the task (Qiwen Mu, 2005). Some confirmed the decreased responses within taskrelated brain regions (Choo et al., 2005; Lange et al., 2005). However, subjects showed diminished performance with fatigue in those studies.

Tasks requiring maintenance of information in working memory elicit bilateral activation in the prefrontal, precentral, and inferior parietal regions, as well as in the insula and thalamus. Tasks requiring the manipulation of information in working memory show more extensive activation in those same areas, reflecting the fact that manipulation requires more cognitive resources than simple maintenance. The studies examining brain function under fatigue during tasks requiring maintenance and/or manipulation of information in working memory have reported both increased and decreased activation with fatigue. Some of that inconsistency can be attributed to the task difficulty, similar to the verbal learning studies. More specifically, tasks requiring only the maintenance of information in working memory are more likely to show deceased activation, whereas those requiring the manipulation of information are more likely to show increased activation with fatigue. Furthermore, increasing the difficulty level within either a maintenance or manipulation task also results in greater activation during mental fatigue.

Overall, the effect of mental fatigue on the cerebral response to working memory demands remains unclear. It appears that arithmetic demands produce decreased activation under fatigue. The brain response to other working memory tasks probably depends on the specific nature of the task demands and the specific subregions with the prefrontal cortex underlying performance of those specific demands.

Visuospatial functioning

Visuospatial functioning refers to those cognitive processes involved in visual perception of spatial relationships among objects. One example of visuospatial functioning involves the recognition of objects, such as circular line configurations, that have no verbal properties. In imaging experiments using recognition of nonverbal objects, visual association areas in the ventral visual stream are commonly activated along with the precuneus, an area associated with the dorsal visual stream. As with working memory tasks, studies using visuospatial tasks have shown both increases and decreases in cerebral activation following mental fatigue. Most commonly, activation in the visual association cortex and precuneus decreases under fatigue, and this correlates with decreased behavioral performance. Regions showing increased activation during recognition of nonverbal objects under mental fatigue include the basal ganglia and insula.

2.4.2 Monitoring mental fatigue

Together with the growth of mental fatigue study, extensive research has been conducted to develop fatigue countermeasure for the purpose of preventing fatigue related accidents using different techniques.

One of simple way to monitor fatigue is to observe the individual behavior. Literature has showed that people experiencing fatigue show some easily observable visual behaviors from the changes in their facial features like the eyes, head, and face. Typical visual characteristics observable from the images of a person with a reduced alertness level include a longer blink duration, slow eyelid movement, smaller degree of eye opening (or even closed), frequent nodding, yawning, gaze (narrowness in the line of sight), sluggish facial expression, and drooping posture. Naturally, computer vision can be a nonintrusive technique for extracting visual characteristics that typically characterize a driver’s vigilance from the images taken by a camera of eyes tracker placed in front of the user. Many studies on developing image-based driver alertness using computer vision techniques have been reported in the literature. Some of them focus primarily on head and eye tracking techniques using two cameras. The method presented in (Matsumoto and Zelinsky, 2000) estimates the head pose and gaze direction. It relies on a two-dimensional (2-D) template searching and then a three-dimensional (3-D) stereo matching of the facial features. A 3-D model was then fit and minimized using virtual springs, instead of the least-squares fit approach for determining the head pose. Another method (Victor et al., 2001) was presented based on a stereo template matching system to determine some specific facial features. A least squares optimization is done to determine the exact pose of the head. Two eye trackers calculate the eye-gaze vector for each eye; these vectors are combined with the head pose to determine the gaze direction. In 2004, a system called FaceLAB developed by a company called Seeing Machines is presented. This is an evolution of the two previous studies. The 3-D pose of the head and the eye-gaze direction are calculated in an exact way. FaceLAB also monitors the eyelids to determine eye opening and blink rates. With this information, the system estimates the driver’s fatigue level. The system operates at both day and night, but at night the performance of the system decreases.

The advantages of these methods are that they are not intrusive, can be fully autonomous. However, it is based on passive vision techniques and its functionality can be problematical if external environmental factors such as lighting, camera position are not stable. Furthermore, segmentation and image processing procedures require a considerable amount of time to analyze user behaviors and therefore, they do not work with the so called microsleeps—when a drowsy driver falls asleep for a few seconds on a very straight road section without changing the lateral position of the vehicle (Ueno et al., 1994).

Beside behavior observation, physical indicators such as heart rate, pulse rate, skin conductance and respiration have been also used to monitor mental fatigue. However, these techniques require electrodes to be attached to the drivers, causing annoyance to them and less applicable in practice. One example for these techniques is the MIT Smart Car (Healey and Picard, 2000), where several sensors (electrocardiogram, electromyogram, respiration, and skin conductance) are embedded in a car and visual information for sensor confirmation are used. In the advanced safety vehicle (ASV) project conducted by Toyota (Kircher et al., 2002), the driver was asked to wear a wristband in order to measure his heart rate. Similar to behavior evaluation techniques, fatigue monitoring approaches based on physical indications suffer from the effects of external environment such as the changes of humidity and temperature.

The Electroencephalograph (EEG) has been acclaimed as one of the most predictive and reliable measurements since it directly reflects human brain state and activity (Mabbott et al., 1999). In the literature, there have been considerable evidences showing the possibility of EEG-based automatic detection of early stages of sleepiness. When one is alert, the brain activities show more fast wave (alpha (8–13 Hertz (Hz)) and beta (13–35 Hz)) activities (Kiymik et al., 2004), while a fatigued individual shows more slow wave (delta (0–4 Hz) and theta (4–8 Hz)) activities(Santamaria and Chiappa, 1987). In a study of night driving, Lal and Craig (Lal and Craig, 2002) found consistent increases in delta, theta, and alpha activity during transition to fatigue from an awake and alert state. Later, other researches established correlation between the low–frequency EEG power and the driving error (Horne and Baulk, 2004; Lal et al., 2003; Papadelis et al., 2006). One possible explanation is that after prolonged waking the cortex switches transiently to a "sleep-like mode". Indeed, during mental fatigue or drowsiness slower EEG activity, including SWA (0.5–4 Hz) or low theta (5–7 Hz) activity, leaks into periods of behavioral waking, and it does so in a region-specific manner (Franken et al., 1991; Leemburg et al., 2010; Vyazovskiy and Tobler, 2005). Consistently, when wake is prolonged beyond its physiological duration, brain metabolism in awake subjects tends to decrease (Everson et al., 1994), as is typical for sleep. The EEG and behavioral manifestations of tiredness seem to occur in a correlated manner, as, for example, caffeine decreased both the rate of buildup of theta EEG activity during sleep deprivation and subjective ratings of sleepiness (Landolt et al., 2004). It was found recently that after sleep deprivation, local populations of cortical neurons in awake rats start undergoing brief OFF periods similar to those occurring during NREM sleep (Vyazovskiy et al., 2011). Thus, even during behavioral wakefulness, local populations of neurons in the cortex may be “falling asleep”, with potential negative consequences on performance, leading to more neurons fire synchronously. However, neither the mechanisms underlying such local and global wake-dependent changes in cortical neuronal activity, nor the neuronal mechanisms underlying behavioral and cognitive deficits after sleep deprivation have been elucidated, complicating the use of the approaches in real-life driving conditions. Additionally, most of current studies used a microscopic analysis of short time-periods to observe the changes in EEG power or waveform signatures immediately prior to sleep onset or performance error. Though some success has been achieved, it can only provide few seconds ahead forecasting.

2.5 Role of thalamus in controlling mental states

Thalamus is the major relay to the cerebral cortex. Is has been describe as the gateway to the cortex. Almost every information about the outside world or about ourselves is based on the messages that have had to pass through the thalamus. The thalamus forms a relative small structure on each side of the midline and can be divided into several distinct cell groups, or nuclei, each concerned with transmitting a characteristics type of afferent signal (visual, auditory, somatosensory, cerebellar, etc…) to a structurally and functionally distinct, corresponding area or group of areas of cerebral cortex on the same side of the brain. The thalamus relates to the largest part of the cortex, the neocortex. Other areas of the cortex, olfactory cortex and hippocampal cortex, are not neocortex and do not receive comparable thalamic afferents, olfactory afferents represent the only pathway of a sensory system that does not have to go through the thalamus before it can reach the cortex.

All areas of cortex receive afferents from the thalamus bringing messages about activity in other neural centers. The best known represent inputs from peripheral sensory receptors or from subcortical neural centers, but these, defined as first order relays, represent a relative small part of the thalamus and cortex, where the major part of the thalamus forms the higher order nuclei; these relay messages to the cortex about the activity in other cortical areas. That is, in addition to the widely recognized direct corticocortical pathway, and it appears that cortical areas are often connected by both pathways in parallel.

The messages that are passed to the cortex through the thalamus involve a minority (less than 10%) of the synapses in any thalamic nucleus. These inputs are called the drivers, and they are glutamatergic and have the characteristic functional properties that define their ability to transmit the message accurately. The great majority of the inputs to the thalamus are modulators, and those that are glutamatergic have properties that compromise the accurate transmission of a message but provide controls for the way the messages is delayed the important of distinguishing the inputs that are drivers from the modulators is crucial not only for the knowing where to look for the messages that the thalamus is sending to the cortex but also for understanding direct and transthalamic corticocortical communication, and communication in any part of the nervous system.

For the first order sensory relays, the message that is transmitted to cortex can be read as signals to be understood in term of temporal distribution of action potentials. These relate closely to the action of the world or the body on sensory receptors. These messages are the link of individual to the world. For most of other thalamic relays, the nature of the messages that thalamus is transmitting to the cortex remains unclear. The thalamic relay can be regarded as a gate for the messages on their way to an area of cortex, either from the outside environment or from other parts of the brain, including other cortical structures. The message can either be relayed or not relayed (gate open or gate closed). And they can be relay in a linear form, when the thalamic relay cells response in tonic mode, providing the cortex with an accurate replication of the information that is received by the thalamus, or in nonlinear for, when the thalamic cells respond in burst mode. The modulation of the relay cells can take many forms, including affecting overall excitability and controlling voltage-gated conductance, those that underlie the burst and tonic firing mode transition. Among the modulatory inputs are GABAergic afferents, mostly from local interneurons and cells of the thalamic reticular nucleus (TRN). These GABAergic inputs are largely responsible for the gating properties of the thalamus. When the GABAergic cells are very active, they will strongly inhibit relay cells that the relay cells no longer fire action potential in response to the drive input. As a result, the gate is shut, leading to the loss of vigilance and attention (Steriade and Timofeev, 2003; Swadlow and Gusev, 2001). This normally happens during inattentive awake, drowsiness or sleep (Steriade, 2001b). On the other hand, if the GABAergic cells are themselves inhibited, the relay cells will respond vigorously to the driver inputs, the thalamic gate is open. This associated with more vigilance (Contreras and Steriade, 1995; Datta and Siwek, 2002).

2.5.1 Thalamocortical connections

As mentioned above, each major thalamic cell groups or nucleus, such as lateral geniculate nucleus (LGN), ventral medial geniculate nucleus (MGN), ventral posterior medial nucleus (VPN), essentially relates to a specific cortical areas, relaying the messages from lower center or from other cortical structures. The bidirectional thalamocortical (TC) network modulates the flow of sensory and motor information to and from the cerebral cortex. The thalamocortical ojection is composed of excitatory relay (glutamatergic).

Thalamocortical neurons are bushy and their variations are linked mainly to soma size, large neurons projecting to deep and middle cortical layers, whereas small neurons project preferentially to superficial layers. TC neurons in relay nuclei receive ascending afferents from sensory and motor pathways. The highest degree of specificity and organization characterizes sensory nuclei, in particular the lateral geniculate, medial geniculate, and ventroposterior nuclei. Motor relay nuclei, ventrolateral and ventromedial, receive afferents from the cerebellum and other structures related to motor functions. Other thalamic nuclei, such as pulvinar and lateroposterior, project to wider cortical areas and are implicated in association processes. Intralaminar nuclei lie within a narrow lamina that separates medial from lateral thalamic nuclei. Distinctly from relay nuclei that receive specific information from sensory or motor pathways, intralaminar nuclei receive afferents from a variety of heterogeneous sources, including fibers from pain pathways, motor centers, and brainstem systems implicated in the control of states of vigilance.

Thalamocortical neurons fire in two distinct modes: tonic and bursting (Lesica et al., 2006; Sherman, 2001; Steriade, 2001b). These modes are invoked in theories of dynamic regulation of sensory information processing in behaving animals, with contrasting views arguing for the optimal transmission of information by tonic firing or bursts. Furthermore, the transition from wakefulness to sleep is demarcated by an increase in the propensity for thalamic bursting and is associated with the expression of spindles, sustained 1–2-s epochs of 7–15-Hz oscillations in neocortex.

2.5.2 The thalamic reticular nucleus

The reticular complex is a thin sheet of neurons surrounds the thalamus. All axons from thalamus to the cerebral cortex and reverse projections from the cortex to the thalamus pass through it. While all of the output neurons of thalamus are excitatory, most of neurons in the reticular complex appear to be GABAergic and inhibitory. Reticular neurons have axons that collateralize within the nucleus and also project to dorsal thalamic nuclei, but not to cortex; they have long dendrites, whose secondary and tertiary branches possess vesicle-containing appendages that form synapses on the dendrites of other reticular neurons. Thus, contrary to TC neurons that can communicate only through intermediary reticular or neocortical neurons, reticular neurons form an interconnected network which is particularly well suited for the generation of some sleep oscillatory types which can occur even in the deafferented reticular nucleus. There is a reciprocal excitatory circuit between glutamatergic neocortical and TC neurons and a recurrent inhibitory loop between TC neurons and GABAergic reticular neurons.

The thalamic reticular nucleus (TRN) is hypothesized to regulate neocortical rhythms and behavioral states. Using optogenetics and multi-electrode recording in behaving mice, Halassa and colleagues (Halassa et al., 2011), for the first time, demonstrated that brief selective drive of TRN switched the thalamocortical firing mode from tonic to bursting and generated state-dependent neocortical spindles. This finding supports the theory that TRN involve in state regulation by regulating the thalamus firing mode. McAlonan (McAlonan et al., 2008) provided evidences that the TRN modulates the brain signal in the thalamus before it reach the cortex, confirming the hypothesis that ‘‘if the thalamus is the gateway to the cortex, the reticular complex might be described as the guardian of the gateway’’ (Crick, 1984).

2.6 Sleep spindles

The wake-to-sleep transition is marked by repeated transitions between an activated, low-frequency and fast, short sequences of low-frequency synchronized waves. This transitional period between waking and sleep is mainly characterized by the appearance of spindle sequences.

Spindles are generated within the thalamus even in the absence of the cerebral cortex (Morison and Bassett, 1945) although the neocortex has a decisive role in the induction and widespread synchronization of this sleep oscillation. Briefly, thalamic reticular GABAergic neurons impose spike-bursts in the frequency range of spindles onto TC neurons, which display rhythmic IPSPs that, when large and long enough, succeed in de-inactivating the Ca^{2+}-dependent current, which produces a low-threshold spike (LTS) crowned by high-frequency bursts consisting of fast, Na^{+}-mediated action potentials. These spike-bursts are transferred to cortical neurons, where they elicit EPSPs, occasionally leading to action potentials. This mechanism, discovered in vivo (Steriade and Deschenes, 1988), was repeatedly confirmed in subsequent experimental and modeling studies (reviewed in Destexhe et al., 2001).

Since the 1980s, evidence has been accumulated demonstrating that reticular neurons are pacemakers of spindle oscillations. The pacemaking role of the reticular nucleus was demonstrated by two major pieces of evidence: (a) spindles disappear in TC systems after disconnection from reticular neurons, and spindle-related long-lasting hyperpolarizations are replaced after disconnection from reticular nucleus by short-lasting IPSPs generated by local interneurons (Steriade et al., 1985) and (b) spindles are preserved within the reticular nucleus disconnected from the remaining thalamus and cerebral cortex (Steriade et al., 1987). These experimental data were corroborated in different types of computational models of isolated reticular neurons, which displayed oscillations within the frequency range of spindles (Wang and Rinzel, 1993).

The concept of causal relations between rhythmic bursts of GABAergic reticular thalamic neurons and cyclic hyperpolarizations of TC neurons underlying spindle oscillations was also supported by in vitro studies in which stimulation was applied to the reticular nucleus at the periphery of the slice and relay cells in adjacent thalamic nuclei were recorded intracellularly (Thomson, 1988). The chloride-mediated IPSPs in TC cells generated by train of pulses to the reticular nucleus gave rise to post-inhibitory rebounds. In contrast to the absence of self-maintained oscillations after current pulses in TC cells, membrane potential oscillations within spindle frequencies were observed after long trains of IPSPs induced by stimulation of the reticular nucleus.

It is known that natural arousal or brainstem reticular stimulation readily blocks spontaneous or evoked spindle waves and transforms the oscillatory mode in TC systems into a relay functional mode, with tonically increased firing rates and enhanced cellular excitability. In addition to the two factors represented by the pacemaking reticular neurons that generate spindles and some intrinsic properties of TC neurons that contribute to the patterning of oscillations, spindles appear as a consequence of dampening activities in brainstem reticular neurons with thalamic projections. Midbrain reticular neurons significantly decrease their firing rates during the transitional period from waking to sleep and reliably slow or completely stop their discharges about 1s in advance of the first spindle sequence and in repeated transitions from EEG-desynchronized to spindling periods during the drowsiness state.

The generalized spindle rhythmicity is under the control of reticular neurons and the mechanism of diffuse spindle disruption by brainstem ascending influxes, as is the case upon natural arousal, should be searched at the very site of spindle genesis, the reticular nucleus. The basic mechanism of generalized spindle desynchronization is probably a decoupling in the reticular network due to a cholinergic hyperpolarization of brainstem reticular origin. The blockage, during natural EEG activation or brainstem reticular stimulation, of spindle-related rhythmic IPSPs and postinhibitory rebound spike-bursts was reported for TC neurons recorded extra- and intracellularly from the dorsal lateral geniculate (LG), lateroposterior (LP), ventrolateral (VL), and intralaminar CL nuclei (Singer, 1973). In lightly anesthetized or unanesthetized preparations, the brainstem-induced blockage of spindle sequences is associated with tonic firing of TC neurons, which may outlast the stimulation period. Under barbiturate anesthesia, however, spindling is blocked without the occurrence of any tonic discharges in TC cells, and a single rebound spike terminates the aborted spindle sequence.

The origin of spindle disruption in TC cells by brainstem reticular stimulation is the blockage of spindles at the site of their generation, the reticular nucleus. Short pulse-trains to the cholinergic pedunculopontine tegmental nucleus (PPT) prevent the occurrence of spindles in the perigeniculate (PG) sector of the reticular nuclear complex or block ongoing spindle sequences. Spindle oscillations of reticular cells develop on a depolarizing envelope. The brainstem cholinergic stimulation induces a large hyperpolarization that blocks the spindles in PG neurons. Measurements of conductance changes associated with the hyperpolarizing response of PG neurons showed an increased conductance of about 40-50%. Since the peribrachial-induced hyperpolarization of reticular neurons is abolished after administration of the muscarinic blocker, scopolamine (Hu et al., 1989), the main mechanism of the spindling blockage by peribrachial (PB) stimulation seems to be a cholinergic hyperpolarization. This assumption is further supported by the fact that data similar were also obtained after amine depletion in reserpine-treated animals. In conclusion then, the blockage of spindle rhythms during EEG desynchronization is due to a decoupling in the synaptic networks of reticular nucleus by brainstem and basal forebrain axons.

In summary, the literature has shown that the key limitation of cognitive fatigue studies is the lack of a neurophysiological approach that can deal with the complex nature of mental fatigue. Although widely used, both subjective assessment and direct measurement of performance might not be adequate to reflect what is happening in the brain under mental fatigue. The use of functional neuroimaging recently has provided new understanding about the neural correlates of mental fatigue, however most of the studies focused on the mental fatigue in clinical populations, which may involve different biological substrates compared to acute mental fatigue in healthy people. On the other hand, recent findings in thalamus study suggested that thalamic reticular nucleus may have the important role in controlling mental states by switching thalamus firing mode. As a result of physiological burst firing mode of TRN in releasing GABA that block connectivity between the thalamus and cerebral cortex, spindles could be an indicator for mental fatigue. Furthermore, less attention has been paid to develop a fatigue intervention method. These set the motivation for the present study.

Chapter 3

General Experimental Methods

This chapter describes the general experimental methods used for mental fatigue monitoring and intervention. The experimental procedure and analysis methods specifically used to achieve specific aims of the study which will be given later in corresponding chapter.

3.1 Experimental methods for fatigue induction

3.1.1 Sleep Deprivation

As one of the major factors which cause mental fatigue, sleep deprivation significantly affects the human health, social activity and economy. Literature showed that sleep deprivation increases of human error related accidents, with such accidents estimated to have an annual economic impact around $50 billion. Additionally, studies of shift-workers, truck drivers, medical students, and airline pilot all show an increased risk of crashes or near misses due to sleep deprivation in these populations.

Sleep deprivation in humans can be broadly classified into three categories: total sleep deprivation (TSD), partial sleep deprivation (PSD), and sleep fragmentation.

TSD is the complete lack of sleep for at least one night or longer. PSD involves restricted sleep for multiple nights, that is, individuals obtaining an inadequate amount of sleep for several consecutive nights. Sleep fragmentation is repeated awakenings from sleep throughout the night. This leads to a decreased amount of sleep but a normal time spent in bed. Most published neuroimaging studies in healthy adults to date have used TSD paradigm.

Since a sleep deprivation experiment is relatively simple to conduct, it has been widely used in studying mental fatigue. Although research on the effects of sleep deprivation on brain function is still in the early stages, sleep deprivation has been reported to impaired cognitive performance due to increasing sleep propensity and instability of waking neurobehavioral functions. Cognitive functions particularly affected by sleep loss include psychomotor and cognitive speed, vigilant and executive attention, working memory, and higher cognitive abilities.

3.1.2 Psychomotor Vigilance Task (PVT)

The psychomotor vigilance task (PVT) (Dinges and Powell, 1985) has emerged as the gold-standard method of assessing changes to vigilant attention stemming from mental fatigue. In this task, a visual stimulus is given and the subject has to press a response button as soon as possible. During the task, the participant’s performance was affected by time-on-task characteristic of mental fatigue, for example mean reaction increase across minutes of the task. Many studies have shown that the reaction time (RT) in this task is directly proportional to mental fatigue level (Lim et al., 2009; Van Dongen and Dinges, 2005).

3.1.3 Simulated driving task

Driving is a complex task involved numerous and varied brain functions such as attention, perception, memory, decision making. A few number of neuroimaging studies have used driving simulators to examine brain activity evoked during driving (Calhoun et al., 2002; Graydon et al., 2004; Uchiyama et al., 2003; Walter et al., 2001). These studies have revealed a network of brain regions more active during driving than rest periods which included the parieto-occipital cortices, cerebellum and cortical regions associated with perception and motor control. Activation in these regions was generally attributed to increased demands on vision, motor skills and visuomotor integration. In addition, activity in frontal, parietal, occipital and thalamic regions was found to correlate with average driving speed (Calhoun et al., 2002). Horikawa et al. (Horikawa et al., 2005) also found that the number of crashes was negatively correlated with activity in the posterior cingulate, while others observed that the ability to maintain a safe driving distance was negatively correlated with activity in anterior cingulate (Uchiyama et al., 2003).

Several studies have shown that prolonged driving time impaired daytime alertness and attention. This could be caused by the combination of two regulatory processes: circadian and homeostatic or by the effects of monotony. More details for this will be presented in chapter 6. Typically, in real life the majority of sleep related accidents occur after at least one hour of driving while performance decrements in driving simulators could be seen much earlier. This could possibly be explained by the lack of stimulation under artificial conditions of driving.

Although, from psychological point of view, results from driving simulator may not be generalized to real-life driving since participants knew that their driving errors in driving simulation would not affect their safety, good correlations between the results of real driving and simulated driving have been demonstrated (Calhoun and Pearlson, 2012; Jeong et al., 2006; Philip P, 2005). Additionally, the safety issues, low cost and ease of data collection are also the advantages of simulated driving.

3.2 Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses strong magnetic fields to create images of biological tissue. The strength of the static magnetic field created by an MRI scanner is express in units of Tesla (one Tesla is equal to 10,000 Gauss). To create images, the scanner uses a series of changing magnetic gradients and oscillating electromagnetic fields, known as a pulse sequence. Depend on the frequency of the electromagnetic fields, energy may be absorbed by atomic nuclei. For MRI, scanners are tuned to the frequency of hydrogen nuclei, which are the most common on the human body due to their prevalence in water molecules. After it is absorbed, the electromagnetic energy is later emitted by the nuclei, and the amount of emitted energy depends on the numbers and types of nuclei present.

Depend on the pulse sequence used, the MRI scanner can detect different tissue properties and distinguish between tissue types. Different pulse sequences can be constructed that create images sensitive to tumors, abnormalities in blood vessels, bone damage, and many other conditions. The ability to examine multiple properties of biological tissue makes MRI an extraordinarily flexible and powerful clinical tool.

The development of fMRI has resulted in an explosion of interest in functional neuroimaging. Most fMRI studies measure change in blood oxygenation over time. Because blood oxygenation levels change rapidly following the activity of neurons in a brain region, fMRI allows researchers to localize brain activity on a second-by-second basis, and within millimeters of its origin. And, because changes in blood oxygenation occur intrinsically as part of normal brain physiology, fMRI is a non-invasive technique that can be repeated as many times as needed in the same individual. Because of these advantages, fMRI has been rapidly adopted as a primary investigative tool by thousands of researchers at hundreds of institutions.

3.2.1 Blood Oxygenation Level Dependent (BOLD) fMRI

In the normal awake human brain, approximately 40% of the O2 delivered to the capillary bed in arterial blood is extracted and metabolized. There is consequently a substantial amount of deoxyhemoglobin in the venous vessels, and so the MR signal is attenuated from what it would be if there were no deoxyhemoglobin. When the brain is activated, the local flow increases substantially, but O2 metabolism increases only by a small amount. As a result, the O2 extraction is reduced, and the venous blood is more oxygenated. The fall in deoxyhemoglobin concentration leads to a signal increase. At 1.5 T, the increase is typically small (a few percent or less). Nevertheless, with careful statistical analysis such small changes can be reliably detected. At higher fields, such as 7 T, the signal changes can be several times larger because the field distortions from magnetic susceptibility effects are proportional to the main magnetic field, so that the same amount of deoxyhemoglobin causes a larger signal reduction.

3.2.2 Experimental design in fMRI

There is a wide range of functional magnetic resonance imaging (fMRI) study designs available for the neuroscientist who wants to investigate cognition. Choosing a right experimental design is probably one of the most critical aspects of fMRI research.

Blocked design

Blocked design is the classic design for an fMRI experiment. In block design, similar stimuli are presented together in a same block, with individual trials or events tightly clustered into "on" periods of activation alternated with equally long "off" control periods. Though simple, blocked design can be extremely powerful and very good for detecting significant fMRI activation. They are easy to create and can be easily explained. However, blocked design are relative insensitive to the shape of the hemodynamic response, lead to it is not useful for estimating the time course of activation in active voxels. Additionally, because of the experimental condition is extended in time, it may evoke highly heterogeneous neuronal activity, making some tasks inappropriate for blocked design.

Event-related design

The second major type of experimental design in fMRI is the event-related design. The central assumption of an event-related design is that the neural activity of interest will occur for short and discrete intervals, as when a brief flash of light evokes transient activity in visual cortex. Stimuli that generate such short bursts of neural activity are known as events.

One advantage of this design is that the estimation of the shape and timing of the hemodynamic are generally better than blocked designs. By characterizing the precise timing and wave form of the hemodynamic response, researchers can make interferences about the relative timing of neuronal activity, about distinct processes within separate parts of a trial, about functional connectivity between regions, and about sustained activation within a region.

However, event-related designs generally have lower detection power than similar blocked design, resulting in part from their sensitivity to the shape of hemodynamic response. If the wrong model for the fMRI hemodynamic response is used, then significant activations may be missed.

In summary, the blocked designs are better for brain activation detection, and event-related designs are better for estimation of impulse response. Therefore, for the purpose of first step in this study, the blocked design was used. The detail of fMRI protocol design for this study was present in chapter 4.

3.2.3 Experimental setup and recording parameters

Functional images were acquired with a 1.5 Tesla scanner (Siemens MAGNETOM Symphony System, Erlangen, Germany) using T2* weighted gradient echo, echo planar imaging sequence, and a blood oxygen level dependent (BOLD) contrast, repetition time 3000 ms; field of view 192 *192 mm and 64 * 64 pixel matrix. 32 oblique axial slices with 3 mm thickness (0.3mm gap) approximately parallel to the anterior and posterior commissure (AC – PC) line were acquired.

3.3 Electroencephalography (EEG)

The discoverer of the existence of human EEG signals was Hans Berger. He began his study of human EEGs in 1920 and is well known by almost all electroencephalographers. An EEG signal is a measurement of currents that flow during synaptic excitations of the dendrites of many pyramidal neurons in the cerebral cortex. When brain cells are activated, the synaptic currents are produced within the dendrites. This current generates a magnetic field measurable by electromyogram (EMG) machines and a secondary electrical field over the scalp measurable by EEG systems. The scalp EEG signal is a temporal and spatial summation of synchronous activations of a number of neurons. It is required the synchronous activity of approximately 108 neurons in a cortical area of at least 6 cm2 to generate measurable EEG (Olejniczak, 2006).

3.3.1 Brain rhythms

In healthy adults, the amplitudes and frequencies of such signals change from one state of a human to another, such as wakefulness and sleep, alertness to fatigue. The characteristics of the waves also change with age. There are five major brain waves distinguished by their different frequency ranges. These frequency bands from low to high frequencies respectively are called delta (< 4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz) and gamma (>30Hz). The delta activity is primarily associated with deep sleep and may be present in the waking state. It is very easy to confuse artifact signals caused by the large muscles of the neck and jaw with the genuine delta response. The theta waves appear as consciousness slips towards drowsiness. Theta waves have been associated with access to unconscious material, creative inspiration and deep meditation. The alpha rhythm is the strongest during relaxation with eyes closed and indicates a relaxed awareness without attention or concentration. Alpha waves have been thought to indicate both a relaxed awareness without any attention or concentration. The alpha wave is the most prominent rhythm in the whole realm of brain activity and possibly covers a greater range than has been previously accepted. Beta waves are the usual waking rhythm of the brain associated with active thinking, active attention, focus on the outside world, or solving concrete problems, and is found in normal adults. A high-level beta wave may be acquired when a human is in a panic state. The gamma activity is generally thought to be associated with higher mental activity like perception and consciousness. The gamma wave band has also been proved to be a good indication of event-related synchronization (ERS) of the brain and can be used to demonstrate the locus for right and left index finger movement, right toes, and the rather broad and bilateral area for tongue movement

3.3.2 Experimental setup and recording parameters

EEG data was acquired using the ANT amplifier system (Fig. 3.1) (Advanced Neuro Technology, Enschede, Netherlands) from 64 electrodes cap (Waveguard EEG cap, ANT) arranged according to the extended international 10-20 electrode placement system (Fig. 3.2). All channels were referenced to the link of the left and right mastoids, and grounded with channel AFz. Input impedances of all channels were kept below 10kΩ for all experimental sessions. Data was sampled at 250Hz and recorded using ASA-lab software from Advanced Neuro Technology.

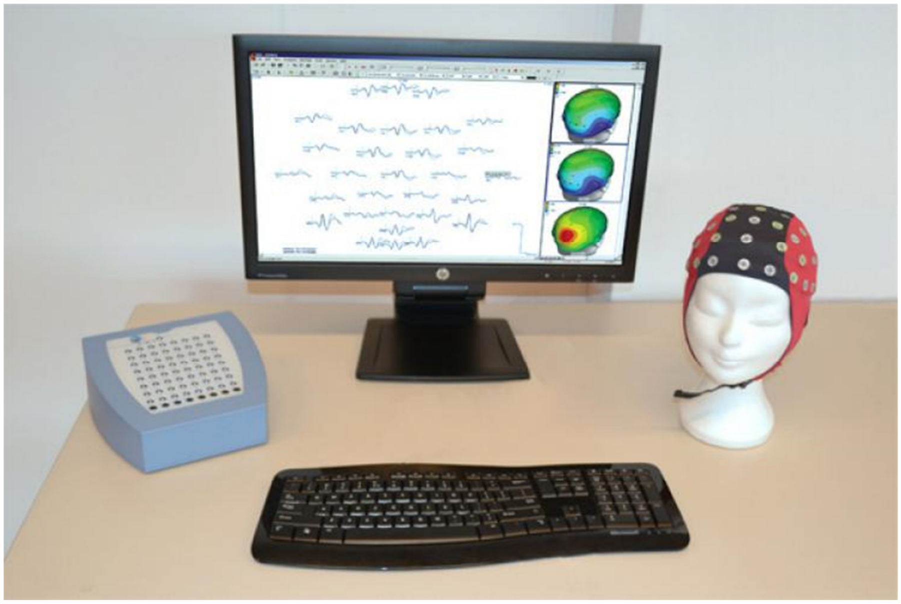


Fig. 3.1: The ANT system used for EEG recording.

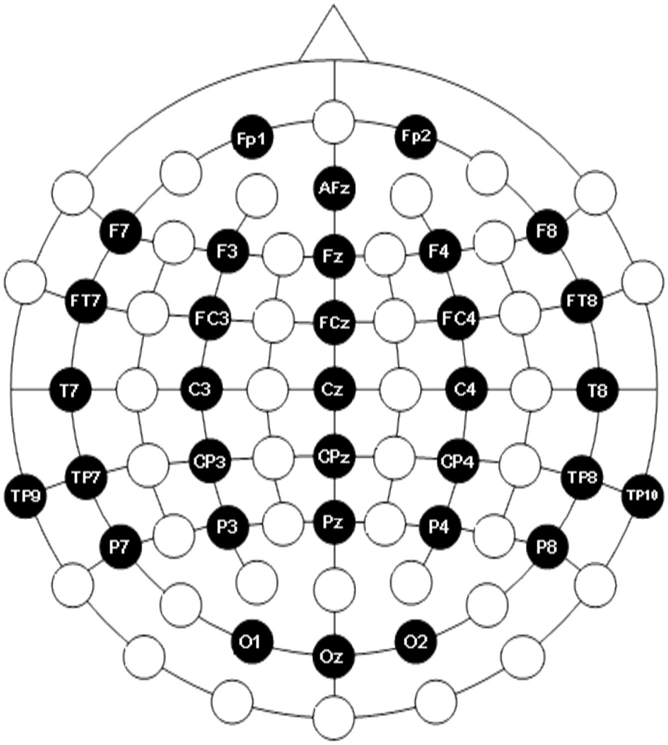


Fig. 3.2. The international extended 10-20 system for EEG electrode placement.

3.4 Trigeminal Nerve Stimulation (TNS)

Trigeminal Nerve Stimulation (TNS) is a novel medical treatment in which mild electrical signals stimulate branches of the trigeminal nerve in order to modulate the activity of targeted brain regions. The trigeminal nerve delivers signals to important structures in the brain, including the nucleus solitarius, the locus coeruleus, the vagus nerve and the cerebral cortex. These areas are known to play key roles in seizure inhibition and initiation. The trigeminal nerve also projects to specific areas along its pathway, such as thalamus and anterior cingulate cortex, which is involved in mood, attention and decision-making.

3.4.1 Trigeminal nerve

Trigeminal nerve has three divisions: ophthalmic, maxillary, and mandibular. The first division, ophthalmic, is the smallest of the three divisions of the trigeminal. It arises from the upper part of the semilunar ganglion and enters the orbit through the superior orbital fissure. The maxillary nerve is intermediate, both in position and size, between the ophthalmic and mandibular. It begins at the middle of the semilunar ganglion and leaves the skull through the foramen rotundum, before terminates beneath the quadratus labii superioris. The third division, mandibular nerve, is the largest of the three divisions. It supplies the teeth and gums, the lower part of the face, and the muscles of mastication.

Trigeminal primary afferent neurons and their associated sensory receptors provide continual information necessary for the perception of changes in the external environment of the oral and facial regions. Of clinical significance, trigeminal neurons mediate a variety of pain states including dental pain, trigeminal neuralgia, temporomandibular joint pain, muscle pain, and headache. In addition to providing general somatosensory information from orofacial structures, trigeminal primary afferent neurons are involved in numerous behavioral responses involving sensorimotor integration at all levels of the neuraxis. Their role in the initiation of relatively simple orofacial reflexes such as the jaw-opening reflex, which is somewhat comparable to the spinal cord flexor withdrawal reflex (Mason et al., 1985), and the jaw-closing reflex, which is comparable to the classic spinal cord myotactic reflex, is well documented. Trigeminal afferent fibers also contribute to other types of sensorimotor integration such as the coordination of the head and neck movements with other parts of the body during complex movement patterns.

Recently, trigeminal stimulation has been applied for treatment of epilepsy, depression, post-traumatic stress disorder and has provided promising results (DeGiorgio et al., 2003; Schrader et al., 2011). The appeal of TNS is that it is a nonsurgical technique and portable. The bilateral stimulation could be advantageous because the central connections of the nerve are both crossed and uncrossed, with rich connections to subcortical structures, including the locus ceruleus, and to cortex via the projections from other subcortical nuclei. The forehead stimuli were well-tolerated with the exception of headache and skin irritation.

3.4.2 Experimental setup

An external pulse generator (Sapphire II, Tecca Medelec, USA) (Fig. 3.3) was utilized to deliver TNS at multiple parameter settings. The electrodes (3M^{TM} Red Dot electrode, USA) were placed on the forehead of the subjects to stimulate V_1 branches of the trigeminal nerve bilaterally. When increased sleep pressure was observed, the stimulation would be delivered for 100s, after that the stimulation was off until sleepiness appeared again.

Fig. 3.3. External pulse generator for trigeminal nerve stimulation

Chapter 4

Neurophysiological Indicator of Mental Fatigue

4.1 Introduction

Mental fatigue refers to the feeling that people may experience after or during prolonged periods of demanding cognitive activity and is characterized by subjective feelings of 'tiredness', 'lack of energy' (Boksem et al., 2006). Along with the increase of demanding mental effort work, these feeling are very common phenomenon in everyday modern life. Mental fatigue has also become one of the most significant causes of accidents nowadays (Dinges, 1995; Lal and Craig, 2001). That is why the study of mental fatigue has been receiving increasing attention from military, transport, health (Caldwell, 2005; Gates, 1916), and occupational risk management (Bailes et al., 2006). However, very little is known about the neurobiological mechanisms underlying mental fatigue. Previous studies based on EEG measurements revealed the neural alterations cause by prolonged periods of demanding cognitive activity in both health and disease subjects (Boksem et al., 2006; Lal et al., 2003; Lorist et al., 2005; Ten

Caat et al., 2008). But, the neuronal activation patterns of mental fatigue were still unclear due to the spatial limitation of EEG. In recent years, functional neuroimaging has been infrequently used to investigate the relationship between objective brain image data and subjective report of fatigue (Cook et al., 2007; de Lange et al., 2004; Lange et al., 2005; Okada et al., 2004). A decisive contribution of functional imaging is that it reveals distributed activation in a way no other method has thus far done. However, majority of these studies focus mainly on fatigue as a symptom of diseases such as multiple sclerosis (MS) and chronic fatigue syndrome (CFS) (reviewed in Chaudhuri and Behan, 2004), which may involve different biological substrates compared to mental fatigue in otherwise healthy people. Recent studies using neuroimaging techniques showed significant associations between mental fatigue and brain activity during a fatiguing cognitive task in several areas including the cerebellum (Cook et al., 2007), the cingulate gyrus (Choo et al., 2005), superior temporal gyrus, inferior frontal gyrus and superior parietal cortex (Lim et al., 2009) and default mode network (DMN) (Sämann et al., 2010). These findings suggested enduring changes in function of these brain areas during mental fatigue, leading to reduced performance or lapses.

Limitation of these prior investigations is that the fatigue scores were obtain based on subjects' self-reports, which is not always reliable (DeLuca, 2005), and they did not show the trend of changes of fatigue state along the increase of time awake and time on task. Furthermore, although multiple neural pathways have been proposed as being involved in mental fatigue, less attention has been paid to investigate the disrupted connection between the thalamus and other brain structures under mental fatigue. Some studies emphasizing subcortical–cortical circuits and dopaminergic projection pathways. Chaudhuri (Chaudhuri and Behan, 2004) suggested mental fatigue is caused by basal ganglia include interrupted connectivity between the prefrontal cortex and thalamus. Another study (Boksem and Tops, 2008) proposed the changes of dopamine influx into the prefrontal cortex alter the ongoing behavior in a way to promote energy conservation or change the focus of attention to more rewarding behaviors. Being considered as a gateway to cortex, the thalamus plays a critical role in integrating, correlating and relaying sensory and motor information to and from the cortex. As we known, the ability of human to speedily respond to environmental changes is fundamentally dependent upon swift changes in neuronal connectivity and excitability. In order to execute appropriate responses, these connectional changes must involve rapid and precise transmission of information between the cortex and the thalamus as well as between cortex areas that are necessary to respond successfully, which seem not available during fatigue. Tomasi and colleagues (Tomasi et al., 2009) reported hyperactivation of thalamus come together with decrease activation of parietal and occipital cortices under sleep deprivation, suggesting thalamus could be the reason underlies the reduced activation in cortical cortices. It is hence reasonable to hypothesize that the dysfunction of susceptible brain regions under mental fatigue may be caused by the functional disruption in the thalamo-cortical connectivity.

Recent studies showed that the thalamic neurons exhibit two distinct modes of firing in different brain states, with tonic spiking during alertness and high frequency rhythmic bursting during drowsiness or inattentive (Steriade, 2001b). In "burst" firing mode, transmission through the thalamus becomes nonlinear, and thalamic nuclei may be functionally disconnected from cortex. These evidences suggest that functional disruption in the thalamo-cortical connectivity could be the results of transitions from 'tonic' firing mode to 'burst' firing mode.

Halassa and colleagues (Halassa et al., 2011) showed that the switch from 'tonic' firing mode to 'burst' firing mode was controlled by thalamic reticular nucleus (TRN) with the expression of EEG spindles. The reticular complex is a thin sheet of neurons surrounds the thalamus. All axons from thalamus to the cerebral cortex and reverse projections from the cortex to the thalamus pass through it. While all of the output neurons of thalamus are excitatory, most of neurons in the reticular complex appear to be GABAergic and inhibitory. As be created by TRN during burst firing, spindles only appear during inattentive awake, drowsiness and early states of sleep. Their occurrence thus constrains many aspects of the communication between thalamus and cortex, ranging from sensory transmission, to cortical plasticity and learning (reviewed in Lüthi, 2013). Additionally, Andrillon (Andrillon et al., 2011) suggested that the level of thalamocortical polarization could be obtained by observing spindles features such as frequency and density. Hence, spindles could be considered as an indicator of disruption in thalamo-cortical connectivity.

The purposes of this study were to investigate the changes of neuronal activation pattern under fatigue and to examine the effects of mental fatigue on thalamo-cortical connectivity as well as the relationship between mental fatigue and EEG spindles. The hypotheses were that mental fatigue does not only cause dysfunction of susceptible brain regions but also alters the thalamo-cortical connectivity and this alteration could be monitored based on spindle activity. The fatigue states hence could also be indicated by spindles.

In order to investigate the effect of mental fatigue on brain activation and brain connectivity, a 24-hour sleepless protocol is used. Functional MRI data of subjects was collected at four time points: in the morning (9 am of the first day and 9 am of the second day), in the afternoon at 2 pm, and late in night at 3 am. Rather than only relying on subjective measures, objective measurement was used in this study. In compared to subjective approaches, objective method has some strong characteristics:

- The amount of skill involved in doing the task is minimal. This will make the task suitable for use without depending on the aptitude or education of a person.
- It has minimum dependence on motivation and other psychological factors, so that it can be more reliable for repeated use.
- The task is sensitive enough to test the functioning capability of a person in a short time, so that it causes minimal disruption of the normal routine of a person.

One of the most commonly methods is the psychomotor vigilance task (PVT) (Dinges and Powell, 1985). In this task, a visual stimulus is given and the subject has to press a response button as soon as possible. Although PVT is a fairly accurate measurement for detecting arousal of a person, it lacks of ability to evaluate other facilities like working memory, judgment and decision-making, which are also affected as fatigue progress. Therefore, to overcome the limitations of previous studies, subjects' fatigue scores were obtained by an objective approach number sequence discrimination (NSD) task in this study. Similar to PVT, NSD is a simple, non-skill-required auditory task. Due to the fact that the auditory dynamics are almost similar to the visual (Dongen and Dinges, 2005), the NSD task is reliable to evaluate subject's vigilance. In addition, the task requires subjects remember briefly a number sequence before keying it out, thus it also access working-memory.

4.2 Materials and methods

4.2.1 Participants

Ten right-handed neurologically healthy subjects (4 females and 6 males; age range 19-25 years old) recruited from the National University of Singapore or Singapore Technology University with the undergraduate education background gave the consent form to participate in the experiment. The subjects were paid for their participation. All subjects were screened using a medical history, a sleep questionnaire, and one week of sleep diary recording to establish that they had relatively regular sleep patterns (sleeping no later than 1am, waking no later than 9am, no habitual daily napping). Volunteers reported consistent sleep-wake cycles in the two weeks prior to the study. All participants were low to moderate habitual caffeine users (less than 250mg per day). They were also non-smokers and free of medication use. Accepted subjects were required to abstain from alcohol-containing beverages and caffeine for 24 h prior to testing and to have sufficient rest the night prior to testing.

4.2.2 Experimental Procedure

The subjects all have to stay awake in National University Hospital totally 25 hours. They were required to report to the laboratory at 8h30am and were monitored onwards for 25 hours without sleep. During the experiment, they were only allowed to engage in non-strenuous activities such as watching television or surfing the Internet, no stimulants of any kind were allowed. For the whole experiment, subjects were scanned at 4 time points (9am, 2pm, 3am, 9am the following day) by fMRI. Before and after each fMRI session, EEG data were recorded to obtain EEG spindle activity. The subjects' level of sleepiness before each fMRI session was evaluated by Epworth sleepiness scale.

In the fMRI scanner, number sequence discrimination (NSD) tasks were presented through earphones at ~95dB. Two runs of the task were administered each time. Each run lasted 6min 42s and began with a 42s starter rest block in which no auditory stimuli was presented, followed by 6 blocks of 30s test block and 6 blocks of 30s rest block. During EEG sessions, subjects were asked to do one run of NSD task.

Number sequence discrimination (NSD) task

The number task involved subjects remembering briefly a number sequence before keying it out. Subjects were first administered a voice recording of a randomly generated number sequence with 1, 2, 3, and 4 played in random order. They were trained before the trial that the index finger denoted a '1', the middle finger denoted '2', the ring finger, '3' and the small finger, '4'. They were required to make a response immediately after hearing the 4 numbers, in which they will press exactly the sequence which they have heard. The duration of each block of stimuli was 3 s and the inter-block interval was 2 s. (Fig. 4.1)

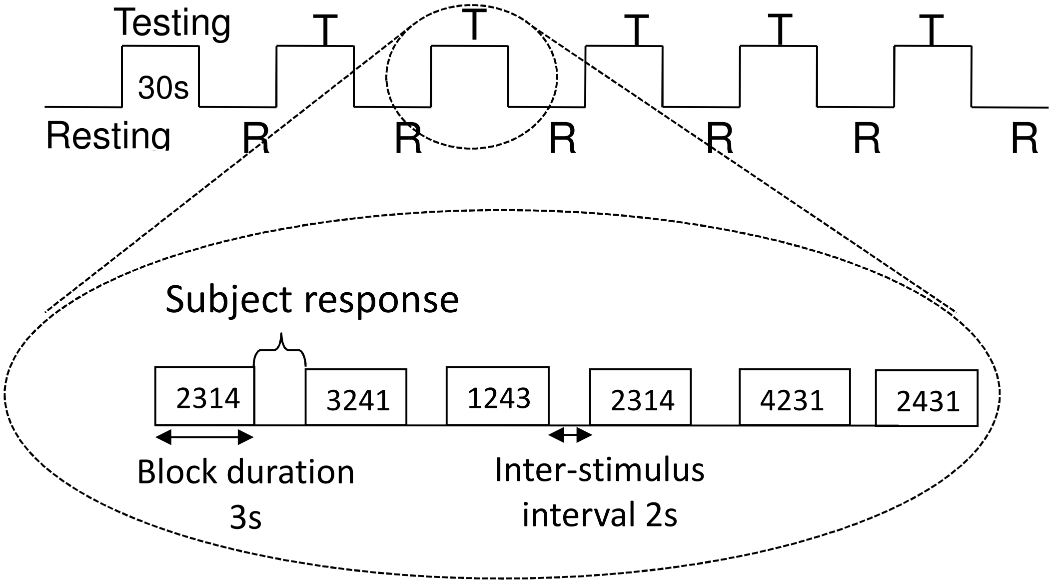


Fig. 4.1 Number Sequence Discrimination Task: Subjects were randomly administered 6 sequences with the numbers 1,2,3,4 in random order in each testing block. They were required to execute the response by pressing exactly what they have heard before the next stimulus was played.

4.2.3 Data Acquisition

EEG signal was collected using Neuroscan NuAmps system from a 32-channel Quick-Cap^{TM} (Compumedics Neuroscan, USA) at sampling rate 250Hz. All channels were referenced to the link of the left and right mastoids, and grounded with channel AFz. Input impedances of all channels were kept below 10kΩ for all experimental sessions. Functional images were acquired with a 1.5 Tesla scanner (Siemens MAGNETOM Symphony System, Erlangen, Germany) using T2* weighted gradient echo, echo planar imaging sequence, and a blood oxygen level dependent (BOLD) contrast, repetition time 3000 ms; field of view 192 *192 mm and 64 * 64 pixel matrix. 32 oblique axial slices with 3 mm thickness (0.3mm gap) approximately parallel to the anterior and posterior commissure (AC – PC) line were acquired. Subjective report of sleepiness level was evaluated by Epworth sleepiness scale.

4.2.4 Data Preprocessing and Analysis

Behavioral Data Analysis

The accuracy and reaction times (RT) were recorded for each subject for the two tasks. In the numbers task, a trial was scored as correct when the subject got all the four numbers in the correct order. A failure to do so or to complete the trial before the subsequent block would be scored as an incorrect response. Accuracy was calculated based on the proportion of trials answered correctly. The reaction time for the numbers task was calculated based on the time lapse taken from when the response was initiated to when the response was completed.

Spindles processing

EEG signals from channels Fz and Pz were analyzed to obtain spindle activity since frontal and parietal cortices exhibited robust spindles detection with densities comparable to those observed in depth EEG (Andrillon et al., 2011). Spindles were detected automatically following previously published algorithms (Clemens et al., 2007; Ferrarelli et al., 2007). EEG spindles were selected based on two criteria: power and duration. EEG signals were band-pass filtered between 9 and 16 Hz (-3 dB at 8.8 and 17.3 Hz) using a zero-phase fourth order Butterworth filter. Hilbert transform was used to compute the instantaneous amplitude of and two thresholds were defined based on this amplitude time course across artifact-free EEG epochs. Potential spindles should have amplitude exceed a detection threshold set at mean + 3 SDs. A start/end threshold was set at mean + 1 SD and events whose duration was between 0.5 and 2 s were further considered. Detections within 1s were merged as single events. Next, only events in which power increases were specific to the spindle frequency range (11Hz-16Hz) were chosen for final analysis. For analysis of detected spindles, spectrograms were computed in ± 1 s intervals around peak spindle power, using a short-time Fourier transform with a window of 744 ms and 95% overlap.

Functional imaging analyses

i) First-level Analysis

The fMRI data is grouped based on the mental fatigue levels which were obtained before each fMRI session. Pre-processing of fMRI data were performed using SPM5 (Friston K.J., 1995) (Fig. 4.2). Images were corrected for slice timing and for motion, and then spatially normalized to the Montreal Neurological Institute template and smoothed using an 6-mm full-width-at-half-maximum (FWHM) Gaussian kernel. Single subject analyses were performed by linear regression of the fMRI data with the boxcar designs, convolved with a standard model of the hemodynamics. A general linear model (GLM) was specified for each participant to investigate the effects of interest, generating parameter estimates for all encoding trials. Statistical parametric maps were created for each subject by applying linear contrasts to the parameter estimates for these events of interest, resulting in a t-statistic for every voxel.

ii) Second-level Analysis

A whole-brain random effects analysis was performed to assess group differences. Between-group differences were tested using an ANOVA *F* test with variances assumed unequal between groups. To characterize among group differences, post hoc two-tailed *t* tests were performed on parameter estimates.

Region of interest (ROI) analysis was also conducted to calculate quantitative regional HRF changes and discover whether regional HRF changes were correlated with mental fatigue deficits. Time series were calculated as the mean signal of all voxel in a 12mm sphere centered around the ROIs, extracted using the SPM toolbox Marsbar (Brett et al., 2002).

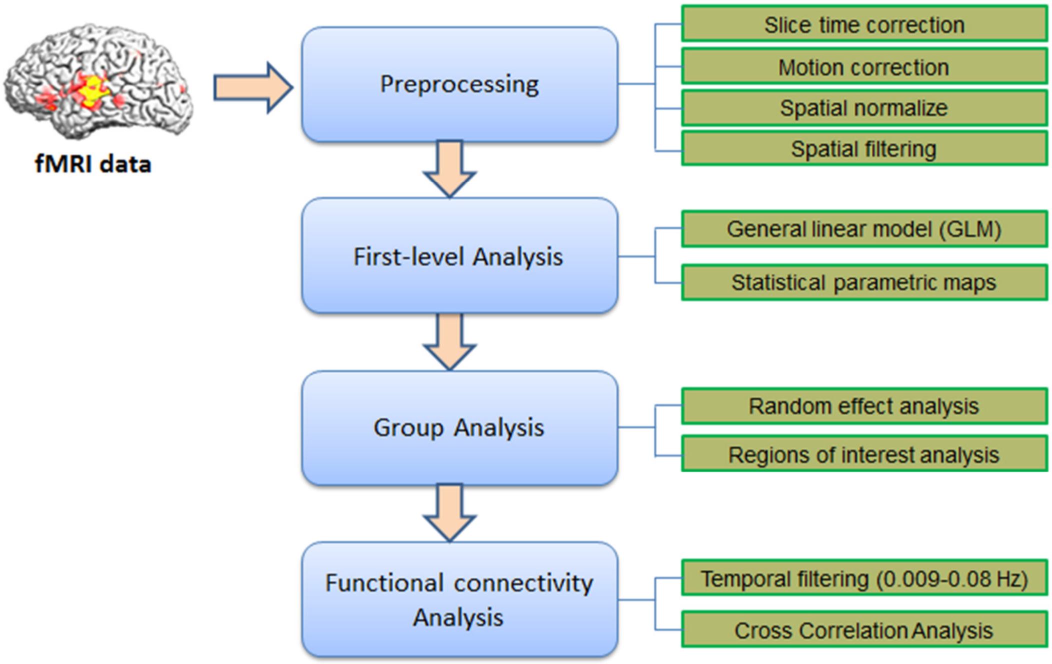


Fig. 4.2. Diagram of functional imaging analysis

iii) Functional connectivity Analysis

For each participant, functional images of resting periods were extracted and temporally filtered (0.009 Hz<f<0.08 Hz). The thalamus defined from second-level analysis was used as seed for whole brain functional connectivity analyses. Time series were calculated as the mean signal of all voxel in a 12mm sphere centered around the thalamus (-9, -22, 14), extracted using the SPM toolbox Marsbar (Brett et al., 2002). Pearson's correlation coefficients were calculated between the time series of the thalamus and every voxel in the brain, for each subject separately, to produce correlation maps. Then Fisher's r-to-z transformation was used to convert these correlation maps into z maps.

$$z = \frac{\ln(1+r) - \ln(1-r)}{2}$$

Group effects then were tested with random-effects analyses using Matlab 7 (Mathworks) and the Statistical Parametric Mapping 5 software (SPM5) (http://www.fil.ion.ucl.ac.uk/spm/) at each time point. The functional connectivity maps collected were overlaid on the standard image with MRICro software (Rorden and Brett, 2000).

The brain areas which showed significant correlation to thalamus during wakefulness (first two sessions 9am and 2pm) were used as seeds (Table 4.3) for further analysis to exam the effect of mental fatigue on thalamic connectivity. Alteration in functional connectivity between thalamus and these seeds were determined by cross correlation analysis.

4.3 Results

4.3.1 Behavioral results

Subjects reported significantly higher sleepiness prior to the 3rd and 4th sessions than the first two sessions (ESS score 1st session 4.3±0.82, 2nd session 2.6±1.19, 3rd session 11.2±2.5, 4th session 10.3±1.43). Prolonged time awake also resulted in slower response time as well as decline of response accuracy (Table 4.1), although repeated ANOVA failed to establish any significant difference in the response accuracy between sessions.

Table 4.1. Behavioral data from NSD task during the fMRI sessions. The results showed the increase of mental fatigue at 3am and 9am second day. Value indicates mean ± SD. ESS: Epworth sleepiness scale.

	9am	**14pm**	**3am**	**9am**
ESS	4.3 ± 0.82	2.6 ± 1.19	11.2 ± 2.5	10.3 ± 1.43
Accuracy (%)	94.61 ± 2.98	97.21 ± 3.05	87.83 ± 12.41	88.88 ± 12.81
Response time (s)	1057.04 ± 42.55	1054.82 ± 66.22	1203.93 ± 93.76	1202.89 ± 80.25

4.3.2 Neural Correlates of Mental Fatigue

Task-related activation and deactivation

Brain regions were showed significant activation and deactivation to the number task during wakefulness (1st and 2nd sessions) were summarized in Table 4.2 and illustrated in Fig. 4.3. During the task, the primary regions of activity included the bilateral thalamus, the cerebellum, inferior frontal cortex, inferior parietal cortex, middle temporal cortices, left supplemental motor extending into left anterior and middle cingulate cortices. These regions typically associated with auditory perception, working memory, attention and motor control.

Table 4.2. Brain areas showing significant activation and deactivation (with *) to the number task

Hemishere	Brain regions	x	y	z	Peak Z-score	p-value
Left	Inferior frontal	-47	9	26	3.00	0.01
Right	Inferior parietal	39	-40	44	6.92	<0.001
Left	Thalamus	-9	-22	14	3.21	<0.001
Right	Thalamus	9	-22	14	3.22	<0.001
Right	Supplemental motor area	6	2	55	3.15	<0.001
Right	Cerebellum	18	-52	-24	8.97	<0.001
Left	Middle temporal cortex*	-54	-37	3	3.45	<0.001
Right	Superior temporal cortex*	51	-10	-13	3.51	<0.001
Left	Superior medial frontal cortex*	-5	53	25	4.57	<0.001
Right	Orbital medial frontal cortex*	-30	56	-9	5.12	<0.001
Right	Insula*	30	-28	18	2.78	0.002
Right	Precuneus*	15	-43	59	4.35	<0.001

Deactivation was found in the precuneus, insula, superior and orbital media frontal cortices, and the middle and superior temporal cortices. These structures belong to the default mode network, which largely involved in integration of autobiographical, self-monitoring and resource allocation.

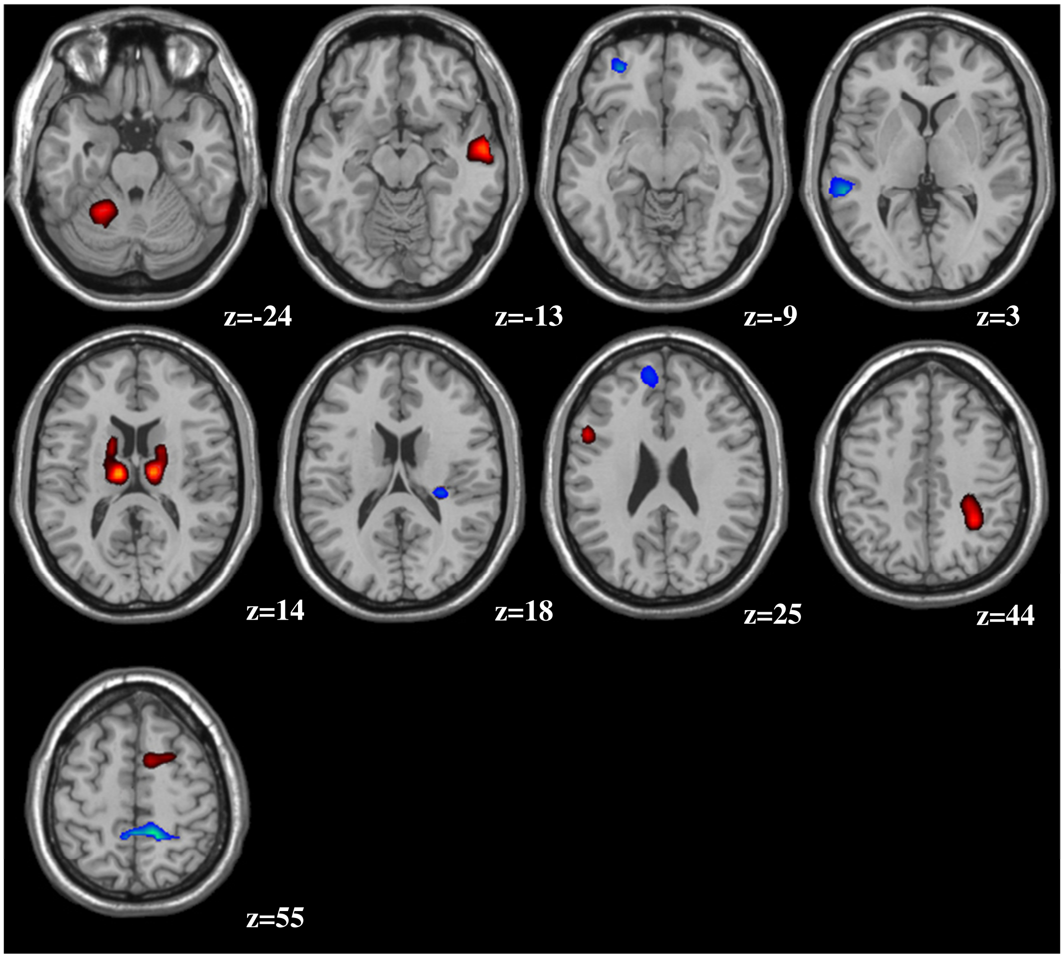
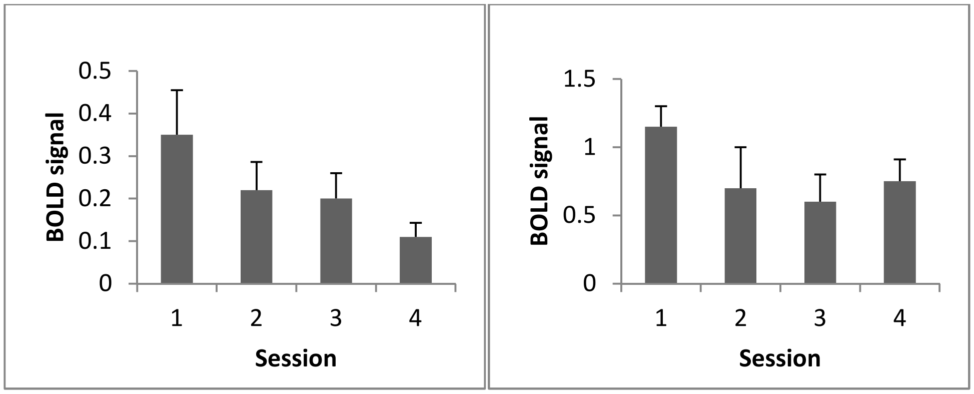


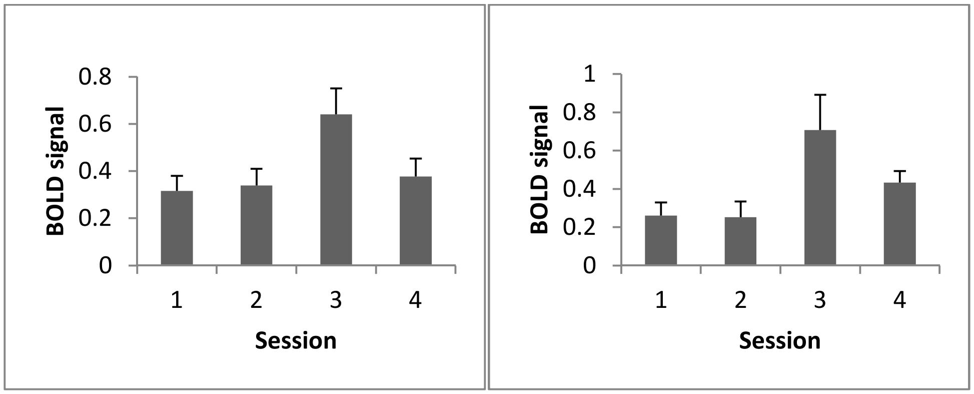
Fig. 4.3. BOLD fMRI activation patterns for the NSD task. Random effect analysis, clusters were thresholded at $p_{FWE\text{-}correlated}<0.05$.

Association of brain activation with mental fatigue

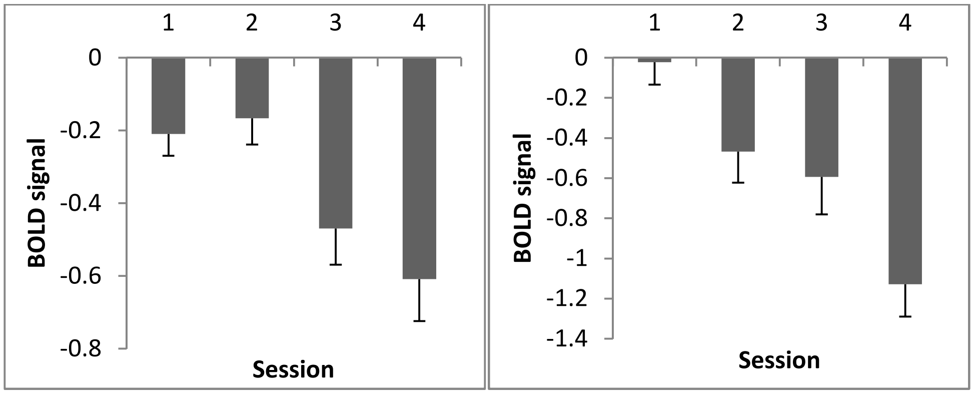
Whole-brain ANOVA revealed significant changes in brain areas between sessions, including thalamus (F(3,36)= 3.07, p=0.04), left inferior frontal (F(3,36)=18, p<0.001) and inferior parietal (F(3,36)=13, p<0.001).



Inferior frontal cortex (-47, 9, 26) Inferior parietal cortex (39,-40,44)



Left thalamus (-9,-22,14) Right thalamus (9, -22, 14)



Precuneus (15,-43,59) Superior medial frontal cortex (-5,53,25)

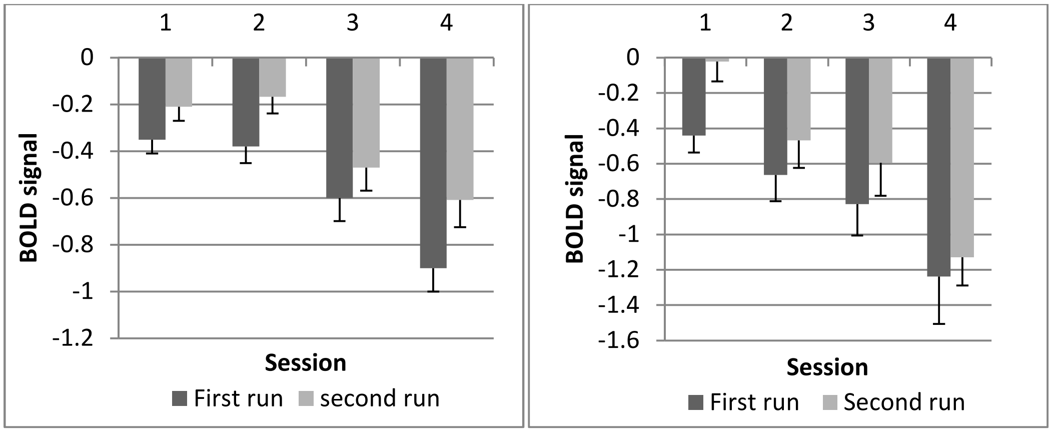
Fig. 4.4. Association of brain activation with mental fatigue. Mental fatigue changed activation in susceptible regions over four sessions. Error bar indicates standard error of mean.

Thalamus activity slightly changed in first two sessions, before increasing in session 3 and then dropped in session 4. Inferior parietal showed opposite trend of change to thalamus, decreased from session 1 to session 3, then increased in session 4. While activation in left prefrontal cortex decreased with time awake.

Increased suppression in precuneus (*F* (3, 36) = 8.62, p<0.001) and superior medial frontal cortex (F(3,36)=5.323, p=0.004) were also observed. Along with the increase of time awake, precuneus exhibited more suppression (Fig. 4.4).

Effect of work-induced fatigue on brain activation

The effect of work-induced fatigue was evaluated by comparing the brain activations obtained from the first run to the second run. There was no significant effect of time-on-task in the areas showed task-related activation (prefrontal, parietal cortices and thalamus).



Precuneus (14,-43,59) Superior medial frontal cortex (-5,53,25)

Fig. 4.5. Effects of time on task on activation of default mode network nodes.

However, changes in activation of default network nodes such as precuneus and superior medial frontal cortex exhibited the influences of time on task. With the increase of time on task, these areas showed less task related suppression (Fig. 4.5).

4.3.3 Effect of Mental Fatigue on Thalamo-cortical Connectivity

Reduced functional connectivity between thalamus and brain areas

Voxel-based analysis using thalamus as a seed demonstrated that functional connectivity of thalamus was positive with anterior cingulate cortex, precuneus, medial prefrontal cortex, temporal cortex, supplementary motor area and cerebellum (Table 4.3) during wakefulness (1st and 2nd sessions). When fatigue level increase due to the accumulation of sleep homeostatic at 3am, the thalamic functional connectivity seem to be blocked (Fig. 4.6) and only slightly increased at 9am (2nd day). This was correlated with the trend of change of spindle occurrences (Fig. 4.9).

Table 4.3. List of regions had significant correlation to thalamus during both first session and second session.

				Peak MNI		
	Region	cluster size (voxel)	$p_{\text{FWE-corr}}$	x	y	z
Default mode network	Precuneus (PCC)	29	0.001	1	-46	54
	Left medial prefrontal (LMPFC)	197	0.005	-1	24	46
Sensory	Left auditory (LAud)	31	0.001	-60	-13	14
	Right auditory (RAud)	30	0.003	59	-10	9
	Supplementary motor area (SMA)	21	0.018	7	-23	55
Executive control	Dorsal anterior cingulate (dACC)	28	0.001	2	22	28
	Cerebellum	114	0.001	0	-52	-8

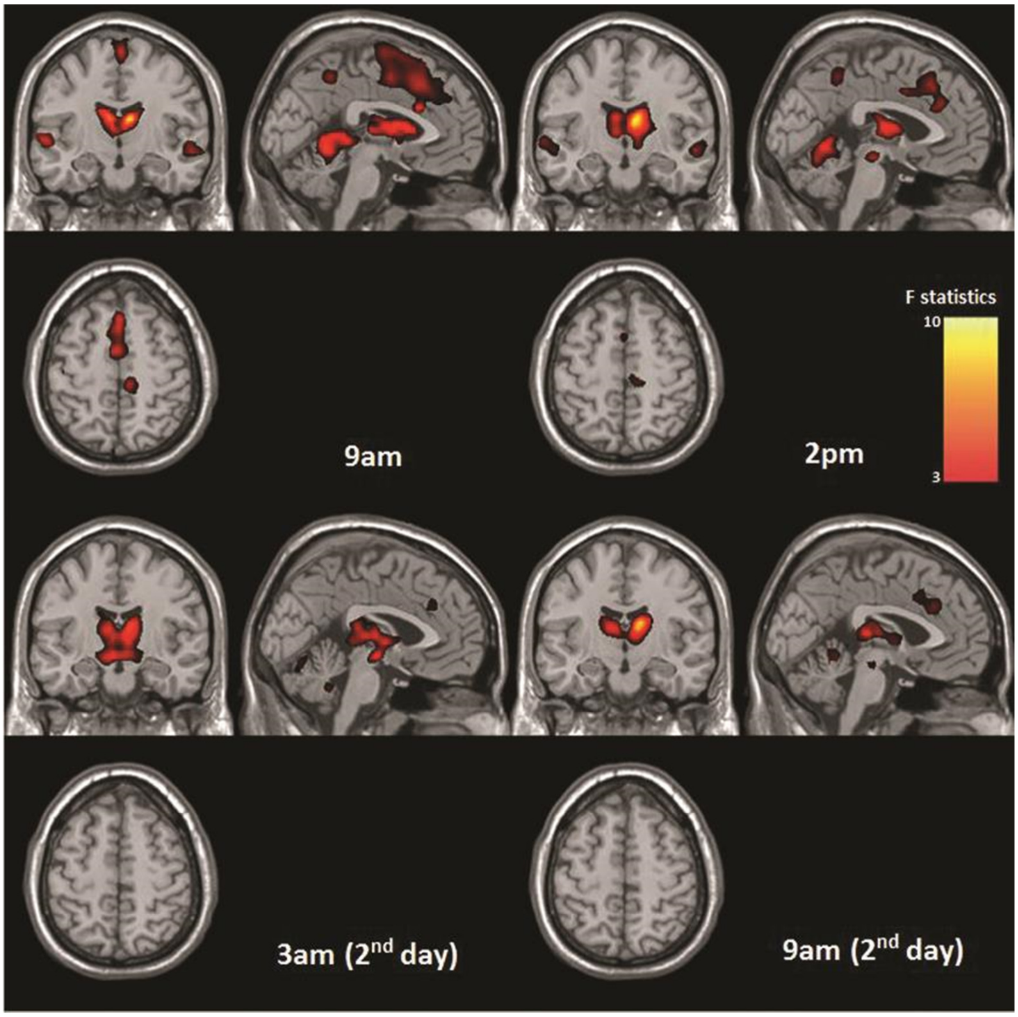


Fig. 4.6: Changes in functional connectivity between thalamus and other brain areas along with mental fatigue level as indicated by spindle occurrences as shown in Fig. 4.9. Thalamic functional connectivity was disrupted when spindle occurrences increased and only increased slightly at the last session when spindles reduced. Clusters were thresholded at $p_{FWE\text{-}correlated}<0.05$.

Figure 4.7 showed the decreased functional connectivity between the thalamus and seed regions determined by cross-correlation analysis. The strength of connectivity between thalamus and these regions were altered when time awake increased. Connectivity to dorsal anterior cingulate gyrus (dACC), precuneus (PCC), supplementary motor area (SMA) and cerebellum decreased from 9am to 3am, especially at 3am, before slightly increased at the end of the experiment

(9am 2nd day). This again confirmed the correlation between spindle occurrences and the disruption of thalamic connectivity under mental fatigue. On the other hand, connectivity to auditory cortex and left medial frontal cortex (LMPFC) decreased along with the prolonged time awake, even during the last session.

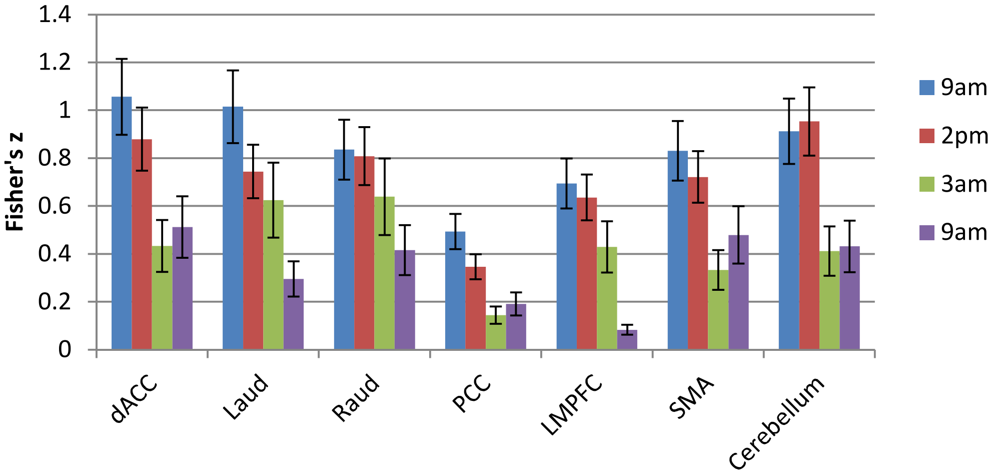
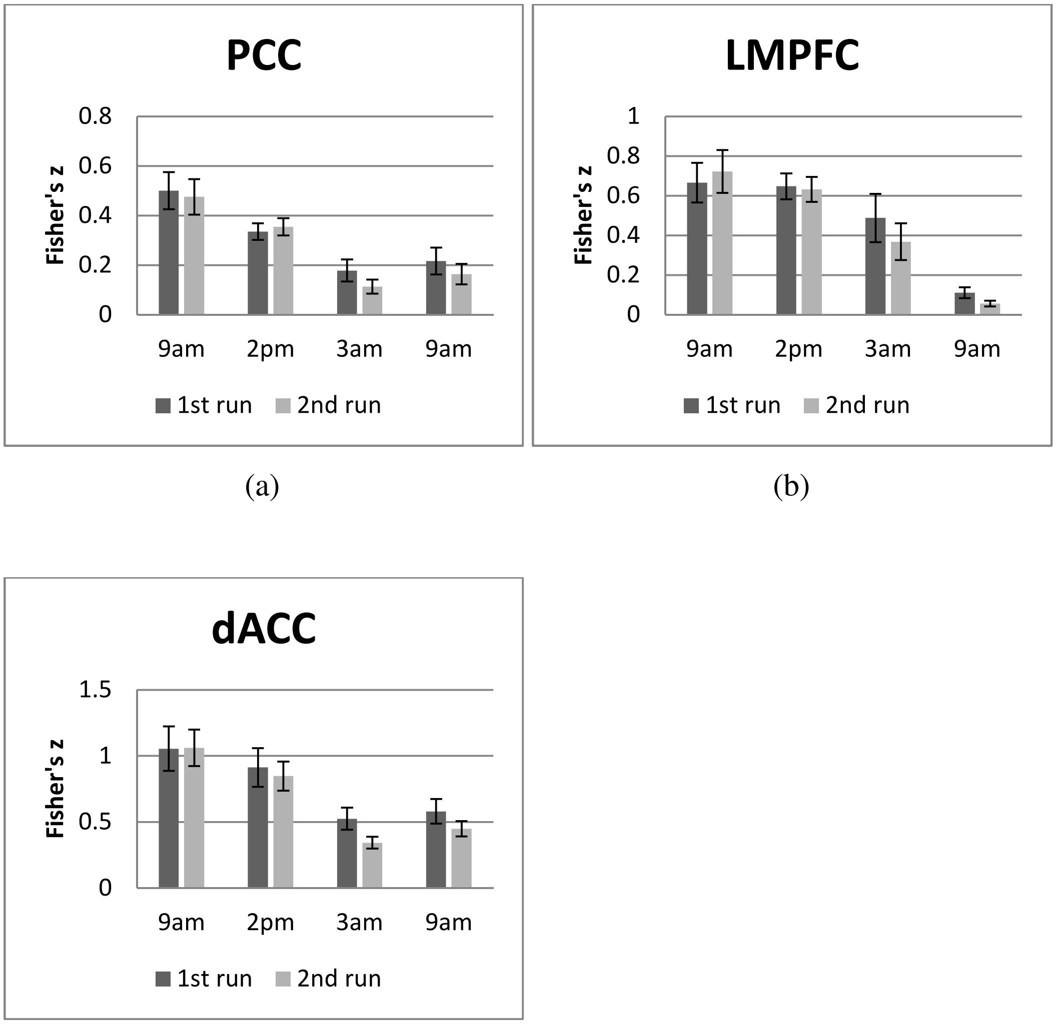


Fig. 4.7: Decreasing functional connectivity between Thalamus and cortex regions under mental fatigue determined by cross correlation analysis. Bars depict means and standard deviation of Fisher's z values. Abbreviation: dACC: Dorsal anterior cingulate, L/Raud: left/right auditory, PCC: precuneus, LMPFC: left medial prefrontal, SMA: supplementary motor area.

Effects of work-induced fatigue on thalamic connectivity to default mode network nodes

Interestingly, differences between 1st and 2nd fMRI runs were found in the strength of functional connectivity between the thalamus and dorsal ACC, the thalamus and the default mode network nodes: left medial frontal cortex and precuneus. As shown in Fig. 4.9, spindles densities are different between pre-task and post-task. This difference was also reflected on the differences between 1st run and 2nd run in thalamic connectivity to precuneus, medial frontal cortex and dACC (Fig. 4.8). The prolonged time on task led to decrease in strength of functional connectivity between the thalamus and these structures. Similar to other results, significant differences mostly appeared at 3am and 9am second day.



(a) (b)

(c)

Fig. 4.8: Differences between 1st run and 2nd run in thalamic connectivity to (a) Left Medial frontal cortex, (b) Precuneus and (c) dACC. The strength of connectivity was weaker at 2nd fMRI run, especially at 3am and 9am second day. Bars depict means and standard deviation of Fisher's z values.

4.3.4 Relationship between EEG Spindles and Mental Fatigue

Spindles occurrences across frontal and parietal region were mostly consistent. As shown in Fig. 4.9, pre-task spindle density at Fz increased along with prolonged time awake, from 0.2±0.24 spindles/min (9am the first day) to 0.82±0.47 spindles/min (2pm) and 4.23±1.37 spindles/min (3am second day), then decreased at 9am second day (3.25±1.14 spindles/min). The post-task results showed similar trend, but the spindle occurrences was higher compared to pre-task's (1st session 0.3±0.38 spindles/min, 2nd session 1.1±0.94 spindles/min, 3rd session 5.98±1.64 spindles/min, 4th session 4.62±1.25 spindles/min). The changes of spindle occurrence were consistent with the alteration in thalamic connectivity, reflecting the inhibition by GABA release on thalamocotical connections under mental fatigue.

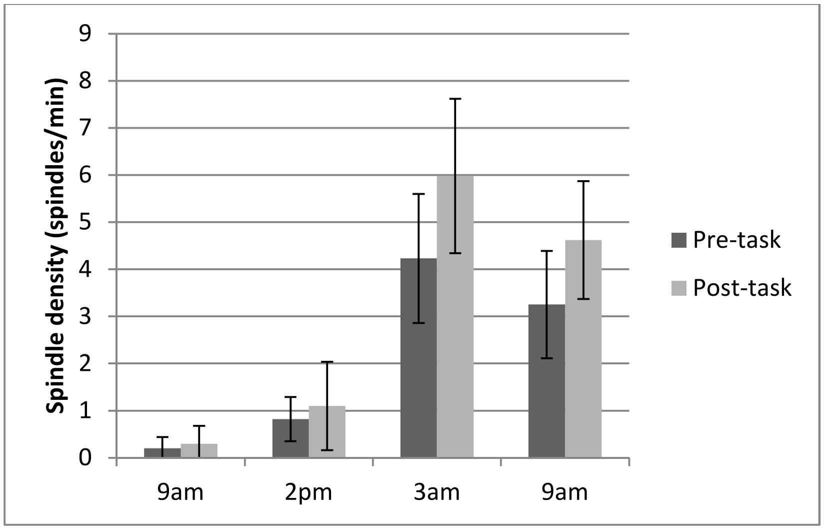


Fig. 4.9: Mean (±SD) spindles density detected at Fz before and after each fMRI session during 24-hours of sleep deprivation.

Repeated ANOVA showed significant differences between session 3 (3am), session 4 (9am 2nd day) and the first two sessions ($p<0.0001$). Spindles density at the last two sessions was similar to densities reported in healthy people during stage 2, stage 3 of NREM sleep (Gaillard and Blois, 1981). Additionally, there were also significant differences between pre-task and post-task spindles density in session 3 ($p<0.006$) and session 4 ($p<0.004$). The changes of spindle density were linearly correlated with performance accuracy during fMRI scans ($r = 0.91$, $p<0.001$); the greater spindle occurrences, the lower accuracy.

4.4 Discussion

The results revealed the effects of mental fatigue on brain activation and thalamocortical connectivity. In general, mental fatigue caused dysfunction of brain activation in susceptible structures such as frontal cortex, parietal cortex, cerebellum, and default mode network nodes precuneus and medial frontal cortex. This dysfunction may be caused by the disruptions in the thalamocortical connections with the expression of spindles. The association of the spindle occurrences to performance accuracy and thalamic connectivity to the cortex suggested that spindles could be a neurophysiological indicator of mental fatigue.

4.4.1 Correlation between brain activation and mental fatigue

This study demonstrates a general pattern for brain activation under mental fatigue. Brain regions that were significantly related to mental fatigue included inferior frontal and inferior parietal cortices, thalamus, default network regions such as precuneus and medial frontal cortex. Prior research indicated these regions have important role in cognitive function, sustained attention, working memory (Bourdaud, 2008; Cook et al., 2007; Lange et al., 2005; Lim et al., 2009). It explains why mental fatigue has widespread effects on attention, working memory and executive control processes. On the other hand, no significant activation was found in Broca's areas, suggesting that language processing and/or comprehension of the task were not affected.

During the task, the inferior frontal cortex was found more active in compared to resting baseline. This may be related to task demands and the effort required for efficient cognitive performance (Rypma and D'Esposito, 1999). However, activation in this area showed negative relationship to level of mental fatigue, the higher fatigue level the less activation. This finding suggests that mental fatigue impairs the ability to store, process information, resulting in the less effective performance of the subjects.

A similar trend of change was found in activation in inferior parietal cortex (from session 1 to session 3). Together with the frontal cortex, it is hypothesized that the fronto-parietal network plays an important role in sustained attention (Lim et al., 2009). In present study, the less active in the network following mental fatigue resulted in performance decline. This result demonstrates the effects of mental fatigue in the attention network. The increase in activation in inferior parietal cortex from session 3 to session 4 may reflect the effect of circadian timing on brain activation.

The thalamus was found to exhibit an increased activation in session 3.The increased activity following mental fatigue is likely to be related to its role in regulating alertness, attention and relaying sensory information to the cortex (Thomas et al., 2001). According to ESS score and spindle occurrences, session 3 was the peak of fatigue. Hence, the subjects would need the most effort to stay awake. The increase in the effort to maintain alertness to perform the task would therefore manifest with the increase in thalamic activity, especially when the thalamic connectivity to the cortex was disrupted frequently under fatigue.

The greater task-related suppression in activation in the default network following mental fatigue was showed in this study. The precuneus node of the default-mode network, which demonstrated greater task-related deactivation in the later sessions, has been proposed to play a pivotal role in how intrinsic activity is mediated through the default mode network (Fransson and Marrelec, 2008). It is suggested that the precuneus forms part of a "fronto-parietal" resting-state network, whose activity is involved in the top–down adjustment and control of task performance, for example, in response to feedback or error signals (Dosenbach et al., 2006). Therefore, it would be reasonable to hypothesize that changes in activation in default network between sessions reflect attempted adaptation or compensation responses rather than dysfunction.

4.4.2 Mental fatigue caused changes in thalamic connectivity

This functional connectivity results showed that mental fatigue also affects the strength of thalamic connectivity to brain structures such as: dorsal anterior cingulate gyrus, region has crucial role in reward-based decision making (Bush et al., 2000); auditory cortex which involves in auditory perception (Cusack, 2005); supplementary motor area, a part of the primate cerebral cortex that contributes to the control of movement; cerebellum, involved in rehearsal procedures sub-serving the phonological loop during verbal working memory (Desmond et al., 1997); and default mode network nodes such as posterior parietal lobe and medial frontal cortex which related to sefl-referential (De Havas et al., 2012; Sämann et al., 2011). Critically, the effects seem to have significant correlation with spindles density measured before and after each fMRI session.

The dorsal anterior cingulate cortex (dACC) involves in variety of cognitive control functions such as monitoring of conflict, error, reward-based decision making, learning. Several studies proposed the conflict-monitoring model of dACC, posited that dACC detects the occurrence conflicts in information processing and relay it to prefrontal cortex to trigger compensatory adjustments in cognitive control. Additionally, the ACC is also considered as the source of Error-Related Negativity (ERN) (Holroyd and Coles, 2002), a component of ERP which occurs after errors are committed during task performance which was significantly reduced in fatigued subjects, while motivating these fatigued subjects resulted in increased ERN/Ne amplitudes (Boksem et al., 2006; Lorist et al., 2005). Boksem (Boksem and Tops, 2008) suggested that ACC receives the reward-related information from basolateral amygdala and orbitofrontal cortex and evaluates these sources of reward information, leading behavior in a particular direction that is predicted to yield the highest reward value. Cerebellum involves both motor and non-motor functions such as language and executive control. Recent investigations provided substantial clinical and experimental support for the role of cerebellum in modulation of affect and emotion (reviewed in Schmahmann, 2000). Dorsal ACC, together with cerebellum, supplementary motor area and thalamus were proposed to form a network to response to the information and adjust cognitive function (Ide and Li, 2011). Another study suggested the cooperation between dACC and the locus coeruleus (LC), the brain stem nucleus that release NA, for encoding information about negative events, outcomes and for behavioral adjustments (Ide et al., 2013). Hence, the decrease in functional connectivity between thalamus and dACC, SMA and cerebellum along with the increase of spindle density under fatigue in this study may reflect the decrease of Ach and NA projection to the brain, resulting in the increased TRN activity and disruption in the flow of information between these regions,.

The decrease in thalamic connectivity to default mode network nodes such as mPFC and PCC correlated with reduced attention and alertness was also found in this study. During wakefulness, default mode network is thought to involve in the intrinsic default brain process (Raichle et al., 2001). DMN is active when individuals are not attentive to the external stimulus but engaged in intrinsic activity such as autobiographical memory and future envisioning (Gusnard et al., 2001). Recent findings showed that functional connectivity between mPFC and PCC is sensitive to vigilance changes and decrease in strength of this connectivity normally leads to the reduced awareness and attention (Horovitz et al., 2008; Sämann et al., 2011; Vanhaudenhuyse et al., 2010). The reduced thalamic connectivity to these nodes together with loss of attention and alertness in this study suggested that the disruption in thalamic connectivity may lead to alteration in direct cortico-cortical connectivity.

Rapid and precise transmissions of information between the cortex and the thalamus are necessary for individuals to respond successfully to changes in external environment. The information can obviously also be sent directly among cortical areas, but using the route through thalamus offers some advantages which are not available in the direct pathway. One crucial advantage of the transthalamic pathway is the ability to modulate, gate the flow of information by GABAergic inputs from local interneurons and cells of the thalamic reticular nucleus. This gating ability also allows the new information from environment reach primary cortical areas so that the brain can continuously monitor the environment, provides information to the cortex about instructions for forthcoming movements. Hence, it is probable that many connections between cortical areas involve parallel pathways, direct and transthalamic, and disruption in the thalamic pathway could lead to impairment in the direct pathway and dysfunction of cortex areas.

4.4.3 Correlation between spindles and thalamic connectivity

The results showed high correlation between the changes in thalamic connectivity and the spindles occurrence. This can be explained by the origin of spindles, the release of GABAergic cells during burst firing. The GABAergic inputs are largely responsible for the gating properties of the thalamus. For instance, if the local GABAergic cells are very active, they will strongly inhibit relay cells that the relay cells no longer fire action potentials in response to drive input. Under these conditions, the thalamic gate is shut and thalamic connectivity is blocked. Alternatively, if the local GABAergic cells are themselves inhibited, relay cells will response vigorously to the driver inputs, and the thalamic gate is open. Intermediate states can be imagined when the level of activity among the GABAergic cell is intermediate.

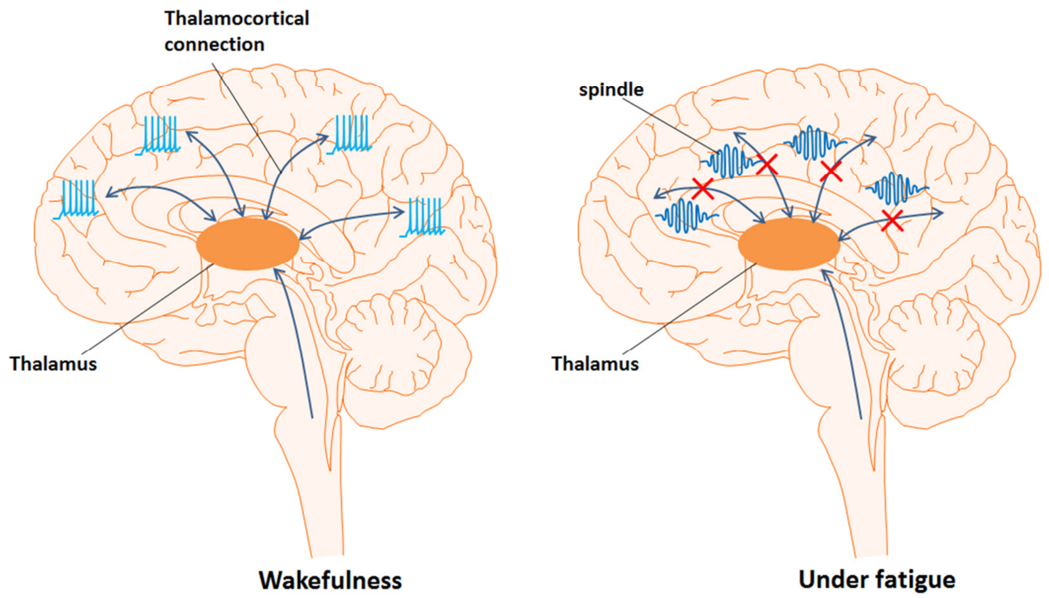


Fig. 4.10. Association of spindles with thalamocortical connections. During wakefulness, GABAergic cells are inhibited, the thalamic gate is open, allowing smooth transmissions of information between cortical areas and thalamus. Under fatigue, the release of GABA, with expression of spindles, strongly inhibits relay cells in thalamus and close the thalamic gate, leading to the disruption in thalamocortical connection.

This correlation suggested that changes in thalamic connectivity can be observed through spindles. This is consistent with Adrillon's observation, which hypothesized that spindles could provide a proxy for the level of thalamo-cortical polarization. Combining with the effects of mental fatigue on the functional disruption in thalamic connectivity, this correlation suggested that spindles could be a promising indicator for mental fatigue.

4.4.4 Spindle occurrence indicated time awake and time on task effects

In general, brain states are affected by time awake and time on task. Prolonged time awake and time on task lead to declines in alertness and attention. These phenomena were reflected by the change of spindles rate in this study. Along with time awake, spindles rate increase as shown in Fig. 4.9. This is expected since TRN activity is affected by the regulation of wake-promoting neurons and sleep homeostatic. During wakefulness, cholinergic inputs from the parabrachial region to thalamus serve to inhibit the GABAergic in TRN via activation of M2 cholinergic receptors on these cells (McCormick and von Krosigk, 1992). As a result, increasing activity of parabrachial neurons disinhibits relay cell, thereby opening the gate, and vice versa. These parabrachial cells become more active with increasing vigilance (Contreras and Steriade, 1995; Datta and Siwek, 2002), and more vigilance is associated with increased responsiveness of relay cell or more opening the thalamic gate. When sleep pressure increased at critical time of day, these neurons fired at low rates, leading to the increase of TRN firing and resulting in more spindles. The decrease of spindle density at the last session (9am, 2nd day) could be a result of increase wake-promoting projection. Be initiating the suprachiasmatic nucleus (SCN - human biological clock) in the morning, neural modulators such as acetylcholine (ACh), noradrenaline (NA) project to central nervous system and inhibit TRN, reducing the number of spindles (reviewed in Lee and Dan, 2012).

Additionally, the effect of work-induced fatigue was clearly shown, with the increase of the spindle densities at post-task compared to pre-task, especially at 3am and 9am second day. While the neurobiology of sleep loss and circadian rhythmicity has been well documented in recent years, the neurobiology of time on task remains vague. This study results suggested the role of TRN activity, represented by spindles, in modulating work-induced mental fatigue.

Spindles are particularly efficient in blocking sensory activation of the cortex and are key elements in the reduced sensory responsiveness during drowsiness and sleep. As the thalamo-cortical system is the major recipient of sensory afferents, changes in its electrical activity will affect the throughput of sensory stimuli. Early studies in vivo demonstrated that the fidelity of retinogeniculate information transfer varied with the state of arousal, and is in particular degraded during periods of drowsiness and sleep (Livingstone and Hubel, 1981), when TC neurons are hyperpolarized and preferentially discharge in bursts rather than in linearly coding tonic trains of action potentials (McCormick and Bal, 1997). Additionally, recent imaging studies looking at auditory cortex activation during sounds showed that activation was essentially nil during spindles, but remained substantial during spindle-free NREM sleep (Dang-Vu et al., 2010; Schabus et al., 2012). Therefore, the abundant occurrence of spindles after prolonged time-awake or sustained time-on-task in this study may plausibly contribute to the lack of cortical response, leading to performance decrements and lapses.

4.4.5 Differences in the effects of time awake and circadian rythm on brain activation and thalamocortical connectivity

It is hypothesized that time awake and circadian rhythms may affect the same neurobiology. Studies based on objective measurement showed a similar trend of change in the subjects' performance following time awake and circadian timing (Lamond et. al, 2005; Dinges et. al, 1997). However, the neuroimaging results in this study showed that there may be some differences between effect of time awake and circadian rhythms. It was showed by the differences in activation and thalamic connectivity at 4th session. While activation in frontal cortex decrease with time awake, the activation in parietal and thalamus may reflect the effect of circadian rhythms. Activity in the thalamus peaked in Session 3, and dropped to a level slightly higher than in session 1 during session 4. The activation in inferior parietal cortex, on the other hand, exhibited an opposite trend. Activation decreased to the lowest value in Session 3, and it increased to a level slightly higher than that of session 1 in session 4. The thalamic connectivity to auditory areas decreased along with time awake, while the rest follows the circadian rhythm. The reason for these differences is not clear and further research is needed.

4.4.6 Impairments of functional domains but also by the compensatory mechanism following mental fatigue

In this study, two different mechanism related to mental fatigue were observed. The first mechanism is the dysfunction of susceptible cortical areas and functional disruption in thalamocortical connections following the increase of mental fatigue level. It suggests that mental fatigue affects the flow of information between thalamus and the cortex and impair cognitive functions such as the ability to store, process information, sustained attention, resulting in the less effective performance of the subjects. Second is the compensatory mechanism, which is indicated by greater activation in thalamus, greater suppression in default network following the increase of time awake. Compensatory mechanism help fatigued subject keep the performance despite the impairment. That could explain for how people are able to uphold performance under fatigue. From experimental studies, it has become clear that even when participants report high levels of subjective fatigue, they can still maintain relative good performance for a long time thereafter.

4.5 Concluding Remarks

In conclusion, this study showed the effects of mental fatigue on the brain activation and the thalamic activity, extending the understanding of mental fatigue. Crucially, this study provided new findings that EEG spindles, as a result of physiological burst firing mode of TRN in releasing GABA that block connectivity between the thalamus and cerebral cortex, vary with mental fatigue levels. Spindles can indicate both circadian and work-induce mental fatigue. The results of EEG spindles measurement of 24-hours sleep deprivation as well as before task and after task provided evidences for these findings. The results of brain activation and connectivity assessments by fMRI further confirm this conclusion.

Chapter 5

Development of EEG Assessment for Monitoring and Predicting Driving Fatigue

5.1 Introduction

Drowsiness/fatigue is a well-known major risk factor for traffic accident. According to data from Australia, England, Finland, and other European nations, drowsy driving represents 10 to 30 percent of all crashes. National Sleep Foundation's Sleep in America (2005) also reported 60% of adult drivers saying they have driven a vehicle while feeling drowsy in the past year, and more than 37% have actually fallen asleep at the wheel. Seriously, of those who have nodded off, 13% say they have done so at least once a month. These numbers may still underestimate the true frequency since it is difficult to assess driver sleepiness objectively (Rosekind, 2005). Moreover, drivers themselves are sometimes unaware of sleepiness (Horne and Baulk, 2004), resulting in the unreliability of subjective assessment.

Extensive research has been conducted to develop systems for monitoring the driver's level of sleepiness using different techniques, such as measures of brain wave, heart rate, electrocardiogram, respiration and eyes tracker. Among these approaches, the Electroencephalograph (EEG) has been acclaimed as one of the most reliable measurements since it directly and immediately reflects human brain state or brain activity (Pack et al., 1995). In the literature, there have been evidences showing the possibility of EEG-based detection of early stages of sleepiness. In a study of night driving, Lal and Craig (Lal and Craig, 2002) found consistent increases in delta, theta, and alpha activity during transition to fatigue from an awake and alert state. Later, other researches established correlation between the low–frequency EEG power and the driving error (Horne and Baulk, 2004; Lal et al., 2003; Papadelis et al., 2006). These studies showed that there are physiologic changes immediately prior to drowsy drivers making errors in driving situations. Based on these findings, several models for detection (Jap et al., 2009; Lal et al., 2003; Papadelis et al., 2007) of drowsiness has been proposed.

However, less attention has been paid to develop a predictor of sleep onset. The lack of research is surprising because an early warning system is essential for avoiding accidents and performance errors. Most of current studies used a microscopic analysis of short time-periods to observe the changes in EEG power or waveform signatures immediately prior to sleep onset or performance error. Though some success has been achieved, it can only provide few seconds ahead forecasting, which may not acceptable in practical. In addition, the mechanisms underlie these changes remain unclear, complicating the use of the approaches in real-life driving conditions (Oken et al., 2006).

This study presents an attempt to overcome these limitations. First, the proposed neurophysiological indicator of fatigue, EEG spindles, was further investigated to confirm if spindle activity could reflect driving fatigue level. Second, a spindle-based fatigue detection and prediction of sleep onset is proposed to allow predicting unintentional sleep onset long time ahead the eventual sleep onset. The proposed method is based on the biological mechanism of sleep instead of the classification methods used in the literature, thus it is more reliable and accurate. This is an important step towards a practically usable countermeasure device for preventing sleepiness or unintentional sleep onset related accidents.

In order to monitor and predict the sleep onset, it is important to understand the initiation of sleep. This section begins with an introduction to the causes of driving fatigue and the effects of monotonous driving, followed by a brief review of the initiation of sleep as well as sleep's hallmark, sleep spindles.

5.1.1 The causes of fatigued and drowsy driving

Driving is a complex task involved numerous and varied brain functions such as attention, perception, memory, decision making. Thus, numerous parameters of given driving situation can affect these processes, complicating the study of driving fatigue (Smiley, 1998). In general, the causes of fatigue and drowsy driving could be classified into two broad categories: endogenous and exogenous factors (Thiffault and Bergeron, 2003b).

The endogenous factors related to the physiological processes underlying alertness or wakefulness, including the circadian variations associated with time of day, the fatigue generated with the duration of the task and sleep-related problems. Long hours spent driving, referred to as the time-on-task effect, is known to produce fatigue and a deterioration of driving performance, although the degradation can also occur during the very early stages of a driving or vigilance task. It is observed that 60% of fatal sleep-related accidents in Finland occurred within the first hour of driving (Summala and Mikkola, 1994). The time-of-day effect is another major factor that accounts for fatigue. From a perspective of sleep-wake regulation, the time-of-day effect is driven by two key neurobiological processes: a homeostatic process producing a progressive sleep drive over time awake and a circadian process producing an opponent wake drive as a function of time of day (Van Dongen and Dinges, 2005). The homeostatic process, known as the sleep "homeostat", balances time spent awake and time spent asleep. While the circadian process, which originates in the biological clock in the suprachiasmatic nuclei of the hypothalamus (Moore, 1995), keeps track of time of day and night. The homeostatic and circadian processes interact to produce a combined influence on driving performance. It was showed that a significant portion of sleep-related accidents happened during the early morning (2am-6am) and during the afternoon period (2pm-4pm) (Pack et al., 1995). Verster et al. (Verster et al., 2011) demonstrated that prolonged nocturnal driving can be as dangerous as severe alcohol-impaired driving. Sleep-related factors such as sleep deficit and sleep deprivation also increase accident risk. Some studies have highlighted that even for short duration of driving (1-2h) and moderate time awake (8h) sleep restriction still can impair driving (Philip P, 2005).

The exogenous factors could be the characteristics of road geometry and roadside environment, or other factors that define the driving task. These factors can have an impact on driving performance by affecting attention, alertness and information processing (Larue et al., 2011; Thiffault and Bergeron, 2003b). It is acknowledged that highway drivers are particularly vulnerable to sleep-related accidents (Åkerstedt, 1994) due to the road geometry and roadside environment remain unchanged or highly repetitive. An under-demanding monotonous road environment with low traffic density can result in feelings of boredom and drowsiness coupled with loss of interest of performing the task at hand, eventually lead to sleep. Performance deterioration, which is induced by under load, may be as important as what is observed during over-demanding crowded urban expressway situations, when arousal is raised to a point where the driving performance is negatively affected.

Endogenous and exogenous factors interact continuously and it is their joint influence that determines alertness and vigilance at any given point during driving.

5.1.2 The initiation of sleep

Sleepiness results in impaired cognitive processing, decreased attention and reduced decision-making capability. Therefore, it adversely affects operators' ability to respond effectively to unusual or emergency situations. According to literature, sleep can be induced by two processes: passive process due to closure of cerebral gates (brain deafferentation) and active process promoted by inhibitory mechanisms arising in some cerebral areas (Steriade, 2001a). These two mechanisms of sleep onset are probably successive steps within a chain of events, and they are complementary rather than opposed (Steriade, 2005).

The passive process of sleep initiation

The passive process of sleep initiation depends on the regulation of homeostatic. Throughout wakefulness, sleep-initiating metabolic factors such as adenosine and neuroinhibitory amino acids (GABA), accumulate in the brain as a result of increased neuronal activity in wake-promoting structures and increased global neuronal activity. When these metabolites reach a critical level, it passively acts on the wake-promoting neuronal systems of the brain to dampen their activities (Datta and MacLean, 2007). The initiation of sleep is a consequence of the dampened activities in our wake-promoting brain systems. After the initiation of sleep, some of these sleep-initiating factors are also involved in the induction of sleep.

Sleep initiation as a result of the active process

Due to the effect of monotonous stimulation, driver becomes habituated (loss of interest). The absence of a steady excitatory bombardment may produce disfacilitation in some brain structures, eventually followed by rebound cellular excitation that would set in motion a series of structures which may promote sleep through active inhibitory processes. The inhibition of GABAnergic cells within the major wake-promoting cell groups: histaminergic cells (HA), noradrenergic cells (NE), serotonergic cells (5-HT), thus leads to sleep through deafferentation, as postulated in the passive theory of sleep.

5.1.3 EEG Sleep spindles as an indicator for mental fatigue

Sleep spindles are groups of rhythmic waves characterized by progressively increasing then decreasing amplitude. Spindles appear during inattentive awake state, drowsiness and early states of sleep in the 11-16Hz band of EEG signals (Fig 5.1). The duration of spindle is between 0.5 and 3s; they start with a sudden increase and end with a sudden decrease in the signal amplitude. Spindles can be categorized into slow (11–13 Hz) and fast (13–16 Hz) spindles according to their frequency. Slow and fast spindles have entirely different topographic distributions on the head; the slow spindles have anterior distribution and the fast spindles have centro-parietal distribution (Cote et al., 2000; Zeitlhofer et al., 1997).

Previous studies revealed that spindle plays an important role in regulation of arousal, and in maintaining a disconnection from the external environment through a “thalamic gate” (Steriade and Timofeev, 2003). As described in chapter 4, spindles have high correlation with fatigue level as well as the change of thalamic connectivity to the cortex. The relationship between spindle activity and performance deficits was also presented in chapter 6. Adrillon et al. (2011) also suggested that a simple non-invasive EEG measure of spindle properties could provide the level for thalamocortical polarization at any given time.

Thus, the generation of spindles can be a marker of the transition from waking to sleep onset and spindle properties such as their spectral frequency, density can be used as features for detecting and predicting sleepiness.

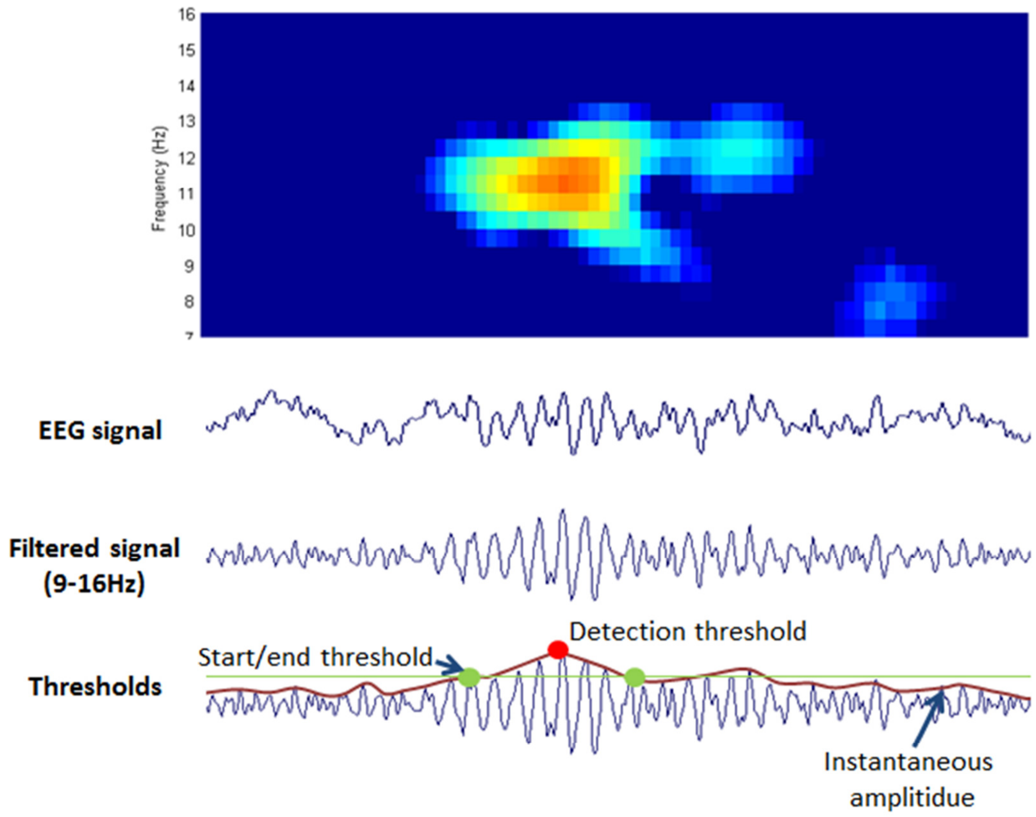


Fig. 5.1. Sleep spindle and its detection. Spindles have frequency in range 11-16Hz, duration from 0.5 to 3s. Spindles detection: spindles were detected based on their power and duration. First, raw EEG signal was filtered in the range 9-16 Hz. Then the instantaneous amplitude (solid line) was obtained by Hilbert transform. After that, a detection threshold and a start/end threshold were used to detect spindles.

5.2 Materials and Methods

5.2.1 Participants

Sixteen young healthy men, range 21–25 years old, participated in the study. All the participants were recruited from the National University of Singapore and Nanyang Technological University, had normal or corrected to normal vision, reported no history of neurological problems and were right-handed. Subjects were required to keep a sleep diary one week prior to the experiment to ensure that they had at least 7 hours of continuous sleeping time and regular sleeping hours (going to bed no later than 1 am and waking up by 9 am). Informed consent was obtained from all participants in accordance with the guidelines and approval of the National University of Singapore Institutional Review Board. The subjects will be reimbursed for each trial for their participation.

5.2.2 Experimental Procedure

All the subjects were tested in the evening from 8pm to 2am next day which is associated with the peak for nocturnal sleep-related accidents. Participants were asked to have dinner early and come to the laboratory at 19:30. The experiment lasted for six hours continuously. Subjects were asked to sit comfortably and avoid unnecessary movements such as singing, mumbling, or talking during the experiment.

Simulated driving task

Simulated driving tests (George, 2003) consisted of a video clip showing moving road images of monotonous highways mostly free of vehicles shown from the perspective of a driver while operating a car. Subjects were instructed to watch the road at all times and respond by pressing keyboard buttons (left and right arrow) when the car changed lanes. The lane changing events were randomly happened each 30s to 2 minutes. Simulated driving lasted for six hours. The participants were asked to try to maintain vigilance and stay awake during the task.

Fig. 5.2. Simulated driving task. Subjects were instructed to watch the road at all times and respond by pressing left and right buttons when the car crosses the middle line.

5.2.3 Data Acquisition

EEG data was acquired using an ANT amplifier (Advanced Neuro Technology, Enschede, Netherlands) connected to a 64 channels cap (Waveguard EEG cap, ANT). EEG electrodes were mounted on the cap based on the extended International 10-20 electrode placement system. All channels were referenced to the link of the left and right mastoids, and grounded with channel AFz. Input impedances of all channels were kept below 10kΩ for all experimental sessions. Data was sampled at 250Hz and recorded using ASA-lab software from Advanced Neuro Technology.

The final system only requires 6-channels EEG headset, 4 channels (Fz, Cz, Pz, Oz) for brain signals and 2 reference channels (Fig 5.3), since spindles can be robustly detected at these areas.

EOG recordings were performed by attaching electrodes above and below the left eye using 3M electrodes (Fig. 5.3B). Subjects' face was continuously monitored by a webcam to obtain facial expression.

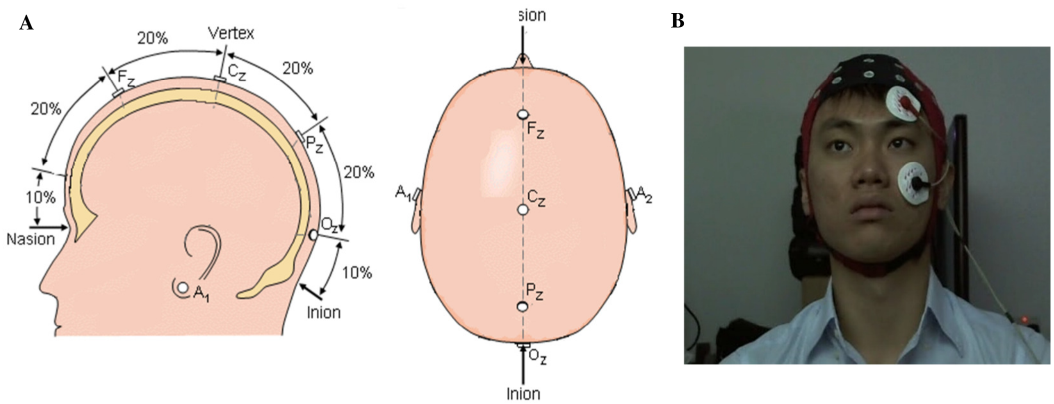


Fig. 5.3. EEG and EOG electrodes diagram. (A) Spindle activity was obtained from 4 channels Fz, Cz, Pz, Oz since the medial areas of the brain exhibited robust spindles detection with densities comparable to those observed in depth EEG. (B) EOG recordings were performed by attaching electrodes above and below the left eye.

5.2.4 Data analysis

Behavioral data analysis

EOG data were extracted for the analysis of eye blinking characteristics, especially blink rates, blink durations and inter-blink intervals. The blink duration was measured from the onset of closure, which was taken as the first downward deflection from the baseline; the end of the blink was taken at the return to the baseline. Video recordings of experiments conducted were analyzed for eyelid closures, particularly the identification of eyelid drooping occurrences. Eyelid drooping (identified at inter-blink periods) was defined by occurrences of eyelids drooping from fully opened positions (i.e. pupils were fully exposed) to half-closed positions (i.e. 50% or more of the pupils are covered). The subject responses were analyzed based on number of lapses and time when lapses happen during the task.

Based on these results, the subjects' visual behaviors were manually scored into 4 fatigue levels each minute and later used to validate the results obtained from EEG signals.

- Level 1 Alert state: fast eye movements with conventional blinks of high amplitude.
- Level 2 Transitional stage: minimal eye movement accompanied by yawning episodes.
- Level 3 Drowsiness onset: slow eye movements and slow blinks dominated, eyelid covered up to 50% of pupil, eye blink period from 0.5s to 1s.
- Level 4 Micro sleep onset: full eye closures lasting longer than 2s.

Spindles detection

Automatic artifact removal (AR) is performed to remove noises, electromyography (EMG) and electrooculography (EOG) artifacts from the raw signals (Kaiquan et al., 2013). EEG signals from 4 channels Fz, Cz, Pz and Oz were then extracted and processed to obtain spindle activity since the medial areas of the brain exhibited robust spindles detection with densities comparable to those observed in depth EEG (Andrillon et al., 2011). Spindles were detected automatically following previously published algorithms (Clemens et al., 2007; Ferrarelli et al., 2007). EEG spindles were selected based on two criteria: power and duration. EEG signals were bandpass filtered between 9 and 16 Hz (-3 dB at 8.8 and 17.3 Hz) using a zero-phase fourth order Butterworth filter. Hilbert transform was used to compute the instantaneous amplitude of and two thresholds were defined based on this amplitude time course across artifact-free EEG epochs. Potential spindles should have amplitude exceed a detection threshold set at mean + 3 SDs. A start/end threshold was set at mean + 1 SD and events whose duration was between 0.5 and 2 s were further considered (Fig. 5.1). Detections within 1s were merged as single events. Next, only events in which power increases were specific to the spindle frequency range (11Hz-16Hz) were chosen for final analysis. The time-frequency map of each spindle were computed in ± 1 s intervals around peak spindle power, using a short-time Fourier (STFT) transform with a window of 744 ms and 95% overlap. The STFT can be calculated as:

$$STFT\{x(t)\}(\tau,\omega) = X(\tau,\omega) = \int_{-\infty}^{\infty} x(t)\omega(t-\tau)\, e^{-j\omega t} dt \qquad (1)$$

where $\mathrm{x(t)}$ is the EEG signal and $\mathrm{w(t-\tau)}$ is the window function.

Upon this point, some fake spindles still exist due to noises which could not be removed by the automatic artifact removal. These noises exhibit consistent characteristics that the spectral power density dominates across the frequency band from 8 Hz to 16 Hz, while the spectral power density of a correct spindle cannot dominate all across this frequency band, e.g. it is only notable between 10Hz and 14 Hz or 13 Hz and 15 Hz. Thus, spindles with the consistent pattern as indicated above, which is the spectral power density dominates across 8 to 16 Hz, are eliminated to a certain threshold.

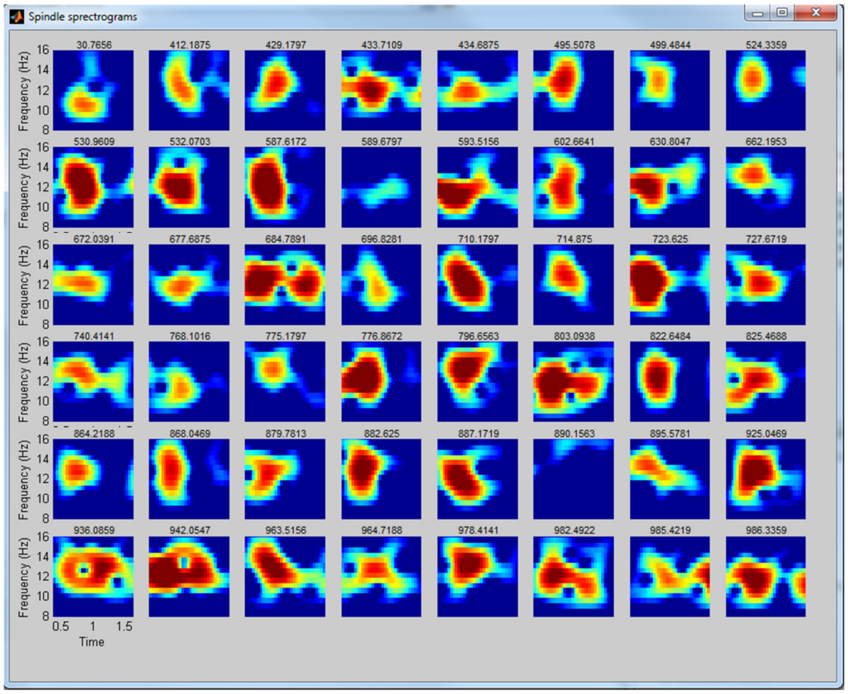


Fig. 5.4. Spectrogram of detected spindles.

The final correct detected spindles were shown in Fig. 5.4. Darker color suggests greater spectral power and therefore tendency to more fatigue and vice versa. This method can detect spindles up to 96% accuracy.

Spindles analyses

For each detected spindle, several parameters were stored for further analysis including start and end times, frequency, and amplitude. The timing of individual spindles was determined as the mean of their start and end times (center), thereby avoiding influence by the choice of the start/end threshold. The frequency of each detected spindle was estimated by identifying the maximal spectral power for each event within the spindle frequency range with a resolution of 0.2 Hz.

The spindle's patterns from data of 3minutes before and 2 minutes after the lapses in performance and data of 1 minute before the micro-sleep events were calculated to use as criteria for fatigue detection.

Fatigue detection and prediction of micro sleep

Based on the results in chapters 4, EEG spindles were chosen as the biological indicator for fatigue. Indeed, when no spindle occurs the thalamic gate is open and the individual is alert. The occurrence of spindles marks the transition from wakefulness to drowsiness (equivalent to level 2 in the manual score). The higher spindles occurrence, the higher of fatigue level. The values of spindle's parameters obtained from EEG data around the lapses were used as thresholds for detecting the onset of drowsiness (level 3 in the manual score). The onset of the micro-sleep (level 4 in the manual score) was defined by the spindles activities calculated from the data prior to micro-sleep events. The relationship between fatigue levels and spindles' parameters was shown in section 5.3.3. The fatigue levels of each minute during the task calculated based on the EEG spindles were then compared to the manual scores of the visual behavior to examine the validity of the method.

The prediction of micro-sleeps is a bit tricky, since the transition from wakefulness to sleep in driving does not follow the normal sleep sequence, which progresses step by step from stage 1 into stage 4 and non REM sleep, as showed in the results section. Under driving conditions, fatigue states could jump between levels, proving to be non-sequential and hard to predict. Therefore, the predictor utilizes a set of past 3 minutes data, instead of 1 minute as in the detection, to obtain a wide pattern of GABA release in order to deal with the abrupt changes in fatigue states. A warning for microsleep onset will be given when the spindles density is higher than 3 spindles/min for 3 consecutive minutes, together with decrease in frequency and increased amplitude.

5.3 Results

5.3.1 Behavioral results

Most of the subjects experienced microsleep multiple times during the test. The participants' time spent before falling asleep was showed in Table 5.2. As can be seen, 12 out of 16 subjects fell asleep the in first hour, this is expected since the combination of monotony (Thiffault and Bergeron, 2003a), effects of simulated condition (Philip P, 2005) and circadian rhythm (Verster et al., 2011) makes the sleep pressure increases faster than usual (George, 2000).

The results showed that the fatigue levels during driving task transited from one to another (Fig. 5.5) and did not follow the normal sleep cycle which progresses sequentially from stage 1 to stage 4. A possible reason for this non-progressive process of the involuntary sleep onset is that subjects were continuously struggling to recover from drowsiness. They were consciously aware that their attention on the road was diminishing and they were trying very hard to sustain and maintain their alertness levels.

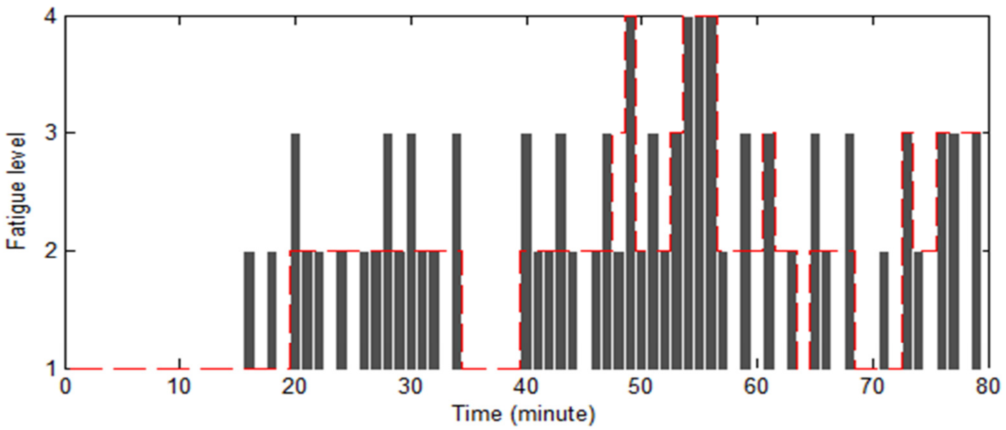


Fig.5.5 Fatigue levels of subject 2 in first 80 minutes. The dash line represents the manual scores using physical results from EOG, facial expression data. The bars indicate the fatigue levels calculated based on spindle activities.

5.3.2 Spindles detection accuracy

The algorithm achieved around 96.36% accuracy (Table 5.1). This accuracy is comparable to other approaches in the literature (Duman et al., 2009; Ferrarelli et al., 2007). Additional, it takes only around 3 minutes to process 6-hour long data, thus this algorithm is feasible for online spindles detection. The algorithm was later used in the online fatigue monitoring in chapter 6.

Table 5.1. Accuracy of spindle detection.

Subject	**Number of spindles**	**Detected**	**Accuracy(%)**
S1	2059	1988	96.55
S2	855	831	97.19
S3	2041	1924	94.27
S4	1146	1127	98.34
S5	914	889	97.26
S6	2052	1952	95.13
S7	1105	1051	95.11
S8	599	567	94.66

S9	925	885	95.68
S10	534	519	97.19
S11	866	830	95.84
S12	790	738	93.42
S13	1067	1029	96.44
S14	906	871	96.14
S15	103	103	100
S16	782	770	98.47

5.3.3 Association of Spindles with Mental Fatigue

Fig. 5.6 showed the relationship between fatigue levels and spindle's parameters. Spindle amplitude, density showed positive relationships with the increase of fatigue level, while spindle frequency showed a negative association. Statistical analysis showed significant differences between level 2 and higher levels (t-test, $p<0.001$) in all 3 parameters, and between level 3 and level 4 (t-test, $p<0.05$) in spindle density. The decrease of spindle frequency is consistent with literature (Andrillon et al., 2011), spindles frequency tends to reduce when the sleep pressure increase. One explanation for the increase of spindle density is that during the transition from wakefulness to sleep in driving, the monotony interferes and tries to block the external stimuli, leading to the increase of spindle occurrence.

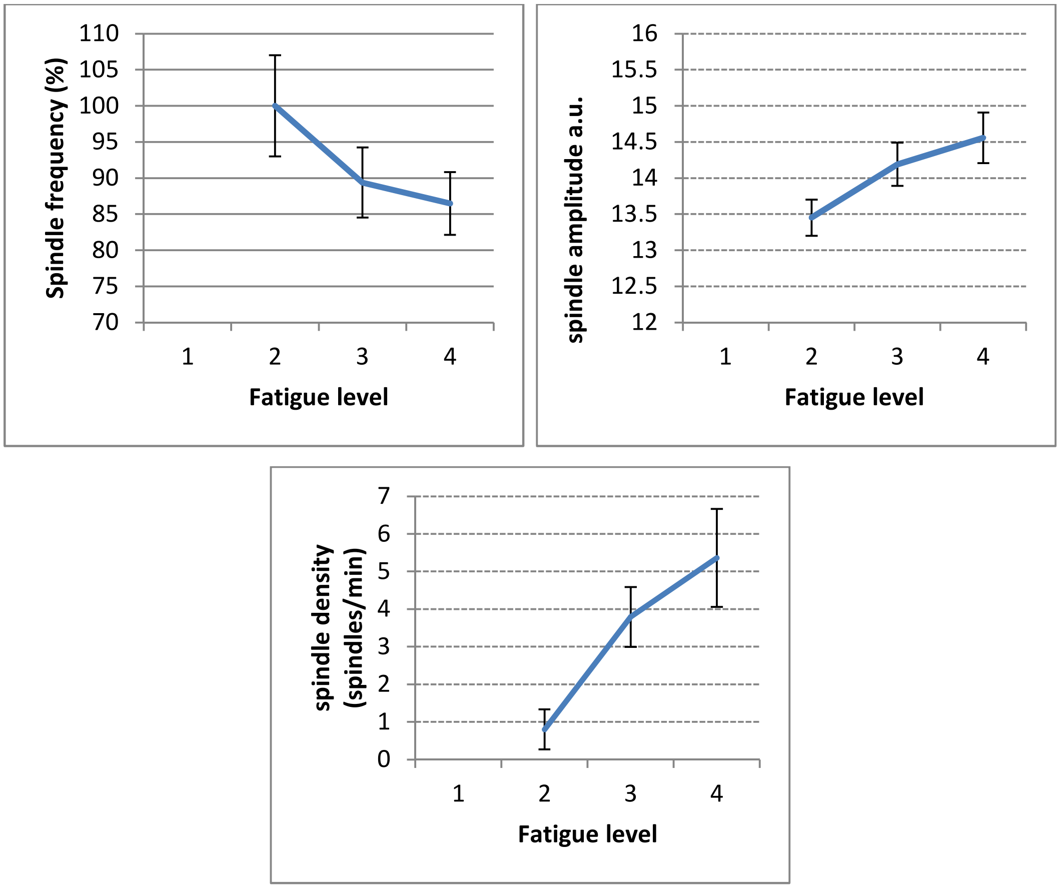


Fig. 5.6. Association of spindles with mental fatigue. The error bars indicate the standard deviation of the means.

5.3.4 Association of Spindles based approach with Visual Behavior Score

Statistical analysis showed a high correlation between the two approaches (r = 0.852; p<0.01) (Fig. 5.7). Fig. 5.5 showed the fatigue levels each minutes of first 80 minutes of subject 2. The bars indicate the fatigue levels calculated based on spindles and the dash line represents the manual scores of visual behavior using results from EOG, facial expression data. As can be seen, the spindles based approach can correctly detect most of the micro-sleep (level 4) and transitional periods (level 2). In addition, it seems to be more sensitive than visual behavior scores in detect the abruptly changes of fatigue level.

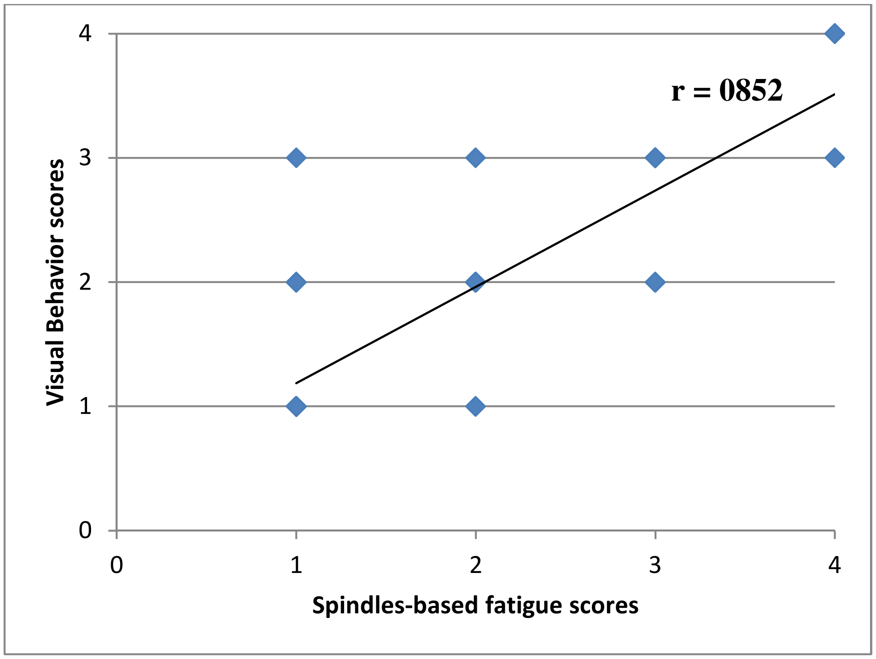


Fig. 5.7. Correlation between Spindles-based fatigue scores and Visual Behavior Scores, ($r = 0.852$; $p<0.01$).

5.3.5 Micro-sleep prediction results

As shown in the Table 5.2, the algorithm could predict the microsleep around 8.4±3.74 ahead with 80% accuracy. The time ahead for subject 5 (1 min), subject 9 (3 mins), and subject 11 (4 mins) is less than 5 minutes, but can still be useful for the warning purpose.

Fig. 5.8 presented a sample of prediction results. Utilizing sets of past 3 minutes data, the predictor gives warning at 45th minute. At 47th minute, the subject showed physical sign of fatigue: eyelid covered 50% of pupil, yawned, eye closure duration around 1s. At 49th minute, the subject dozed off for few seconds.

Table 5.2 Prediction results for the first micro-sleep.

Subject No.	Micro-sleep	Prediction time	Time ahead	Subject No.	Micro-sleep	Prediction time	Time ahead
1	65	51	14	**9**	33	30	3
2	49	43	8	**10**	214	204	10
3	28	20	8	**11**	49	45	4
4	18	12	6	**12**	52	45	7
5	25	23	2	**13**	45	34	11
6	29	16	13	**14**	121	110	11
7	20	14	6	**15**	non		
8	55	45	10	**16**	40	27	13

**All units are minute*

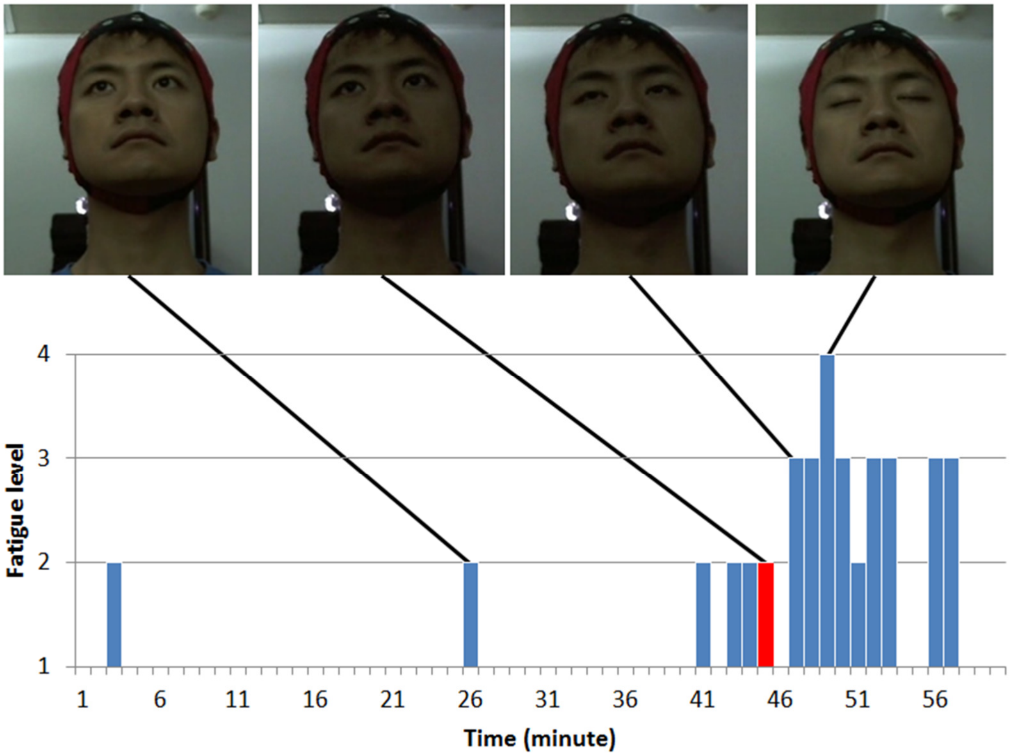


Fig. 5.8. Micro-sleep prediction example (subject 11). The timing of warning was marked as a red bar.

5.4 Discussion

This study proposed a new approach to detect driving fatigue. This approach based on the trend of changes of the spindles along with the increase of mental fatigue. The occurrence of spindles indicates the block of the flow of information to the cortex from sensory cells or from other cortical structures. As we known, driving is a complex task that requires an optimum level of alertness and attention to guarantee the security of the driver and other road users. This optimum level of alertness can only be achieved if the flow of information is smooth, or no spindle is detected. Since spindles only occur during inattentive awake, drowsiness or sleep, the appearance of spindles marks the transition from wakefulness to fatigue. The significant differences of spindles properties such as density, frequency and amplitude between fatigue levels shown in section 5.3.3 provided thresholds for fatigue detection. The consistency between spindles-based detection and visual behavior scores showed the validity of this method.

The increase of spindles density along with the increase of fatigue level found in this study is consistent with the results presented in chapter 4. Due to the absence of a steady excitatory stimulus, disfacilitation in some brain structures was occurred, promoting drowsiness through the release of GABA. The projections of GABAnergic cells to the major wake-promoting cell groups inhibit the activity in cortex areas (Datta and MacLean, 2007), leading to the occurrence of spindles. The more inhibition, the more spindles are produced. This explains for the increase of spindle density.

The changes in spindles frequency could be explained by the role of the level of thamamic hyperpolarization in governing spindles osccillation. Literature (McCormick and Bal, 1997, Steriade 2003) suggested that the degree of hyperpolarization dictates the rate of burst firing. Andrillon (2011) found that the stronger thalamic hyperpolariztion is associated with the lower frequency of cortical spindles. On the other hand, the increasing hyperpolarization is considered to involve in the initiation of synchronized firing of cortex neurons, which is referred as a hallmark for drowsiness (Steriade, 1978). Some study reported the increase of slow EEG waves (delta, theta waves), generated by synchronized neurons firing, under fatigue condition (Lal and Craig, 2002; Vyazovskiy and Tobler, 2005). Hence, the negative relationship between spindle frequency and fatigue level again confirms that a simple measure of spindle frequency can provide important proxy for the level of mental fatigue.

The fluctuated progression of unintentional sleep was also noted in this study. The voluntary recumbent sleep is generally linear, meaning a progression from stage 1 to 4 to REM sleep. In contrast, under the testing conditions of involuntary sleep while driving, progression of drowsiness did not follow this linear progression. Rather, the progression of drowsiness did not follow any particular order. In fact, it was skipping and moving across several levels at a time. This may be due to the struggles to maintain alertness which bring about self-arousals and micro-sleeps that can occur suddenly and unexpectedly.

Compared to manual visual behavior score, the spindle-based approach seem to be more sensitive to the abruptly changes of drowsiness. As shown in Fig. 5.5, the new approach can early detect the onset of fatigue (level 3), which caused lapses in performance, than traditional way. This is because spindles directly reflect the alteration caused by mental fatigue in the brain, while visual behavior can only observe the outcome of this process. This provides the foundation for the fatigue prediction, since accurate feedback of fatigue level at any given time is crucial.

Notably, it should not be forget that these results have been obtained in simulated condition, and the subjects therefore knew that the consequences of their driving errors would not affect their safety and they fell asleep much earlier than in real life driving. Hence, additional larger trials are needed to elucidate efficacy this novel method.

5.5 Concluding Remarks

A novel approach for driving fatigue detection and prediction has been proposed and evaluated.

Since this approach based on neurophysiological indicator of mental fatigue, it is more sensitive and can provide the level of fatigue at any given time. Additionally, it can predict when the drivers have high possibility to experience microsleep long time ahead. Another contribution of this study is that it only needs data from 4 channels Fz, Cz, Pz, Oz to do the detection and prediction. This is important since it simplifies the design of EEG headset, making it more convenient and acceptable in practical. In addition, reducing number of channels also means less calculation time and less required memory for computation, moving a step towards a real-time countermeasure device for preventing sleepiness or unintentional sleep onset related accidents.

Chapter 6

Intervention of Unintentional Sleep Onset Using Trigeminal Nerve Stimulation

6.1 Introduction

Sleepiness and unintentional sleep onset are the common problem for all workers. In American, one of ten people reported that they are likely to fall asleep at an inappropriate time and place, such as during a meeting or driving. The effect of sleepiness is even more significant for people who work in transportation industry. According to National Sleep Foundation's (NSF) 2012 report, one in five pilots (20%) admitted that they have made a serious error and one in six train operators (18%) and truck drivers (14%) reported that they have had a "near miss" due to sleepiness. It has also been identified as the major reason behind fatal crashes and highway accidents caused by car (Hakkanen and Summala, 2000; Philip et al., 2005).

Extensive research has been conducted to develop sleepiness countermeasure for the purpose of preventing fatigue related accidents (Jap et al., 2009; Lal et al., 2003; Papadelis et al., 2006). However, it has been shown that drivers who fall asleep during driving usually underestimate the likelihood of falling asleep and keep driving even though they may aware of their level of sleepiness at the time

(Reyner and Horne, 1998). Therefore, besides monitoring sleepiness, it is also critical to suppress the effect of drowsiness and prevent the unintentional sleep onset.

Clinical and experimental evidences indicated the crucial role of wake-promoting projections arise from upper brainstem neurons; such as cholinergic neurons and noradrenergic neurons, in the induction and maintenance of arousal (reviewed in Saper et al., 2010). These neurons fire robustly during wakefulness, inhibiting the preoptic area, which has significant role in induction of sleep, and suppress the sleepiness. Critically, the firing rate of noradrenergic neurons in locus coeruleus (LC) begin to increase in advance of awakening, suggesting that LC plays an important role in the sleep/waking switch (Takahashi et al., 2010). Literature also demonstrated that the stimulation of the locus coeruleus provokes dopamine release in the cortex such as medial prefrontal and parietal cortices (Devoto et al., 2005). It is hence possible that LC stimulation can prevent individuals from unintentional sleep.

In order to test this hypothesis, trigeminal nerve stimulation was utilized in this study. The neurophysiological mechanism of the proposed trigeminal nerve stimulation in intervening unintentional sleep was presented in Fig. 6.1. Trigeminal Nerve Stimulation (TNS) is a novel approach used to modulate the activity of targeted brain regions by sending mild electrical signals through the trigeminal nerve branches (DeGiorgio et al., 2003; Schrader et al., 2011). The trigeminal nerve conveys information to important structures in the brain, including the nucleus solitarius, the locus coeruleus, the vagus nerve and the cerebral cortex. The trigeminal nerve also projects to specific areas along its pathway, such as thalamus and anterior cingulate cortex, which form a reciprocal connection with LC to modulate mood, error-related cognitive control and behavior adjustment (Ide and Li, 2011; Nakao et al., 2010). Hence, the trigeminal nerve stimulation was expected to be able to suppress the drowsiness by exciting these regions.

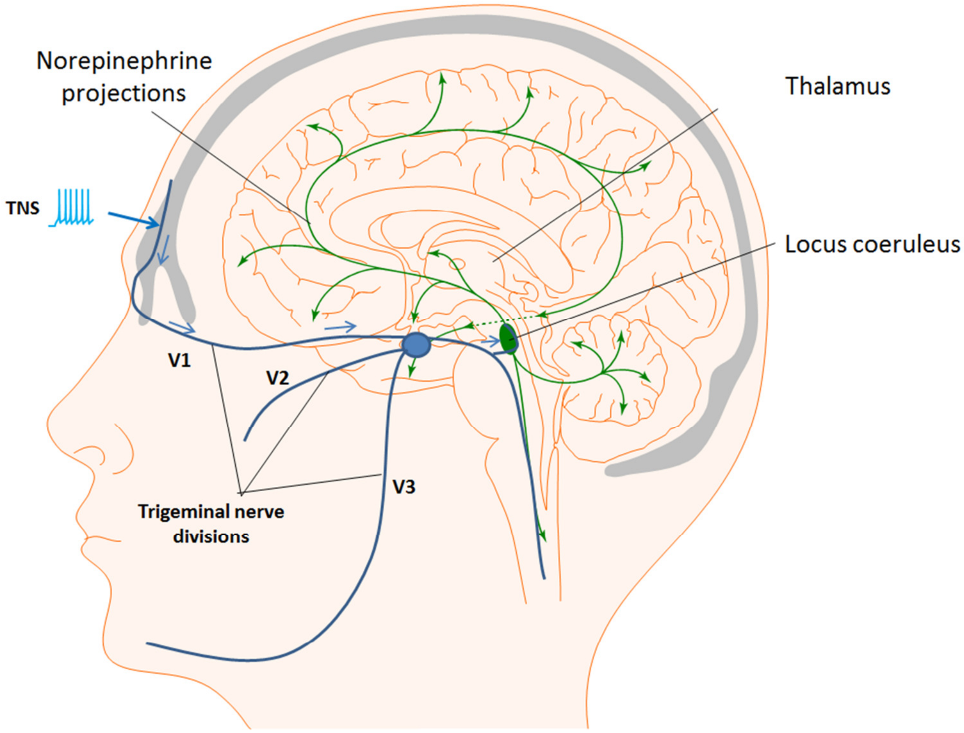


Fig. 6.1. Schematic of trigeminal nerve stimulation in intervening unintentional sleep onset. Electrical stimulation is used to stimulate the V_1 branches of trigeminal nerve. The stimulation is delivered through trigeminal fibers to the locus coeruleus (LC) and excites noradrenergic neurons in LC. Ascending projections originating from the noradrenergic cells travel dorsally to the thalamus to activate thalamo-cortical network and ventrally to the hypothalamus and basal forebrain to activate hypothalamo-cortical and basalo-cortical networks. Activation of these brain regions enhances activation of the cortex as well as global activation of the brain to promote and maintain wakefulness.

6.2 Methods

6.2.1 Participants

Thirty healthy men, range 21–25 years old, participated in the study. Twenty subjects did the assigned task without any stimulation for control data and ten subjects with the TNS. All the participants were recruited from the National University of Singapore and Nanyang Technological University, had normal or corrected to normal vision, reported no trigeminal neuralgia, no history of neurological problems and were right-handed. Subjects were required to keep a sleep diary one week prior to the experiment to ensure that they had at least 7 hours of continuous sleeping time and regular sleeping hours (going to bed no later than 1 am and waking up by 9 am).

6.2.2 Procedure

Participants were asked to have dinner early and come to the laboratory in the evening from 7pm to 9pm. During the experiment, they were requested to do the Psychomotor Vigilance Task (PVT) (Dinges and Powell, 1985) for 1 hour in a dark room. All unnecessary movements such as singing, mumbling, or talking should be avoided during the experiment. The subjects' reaction time and facial expression were recorded.

In the TNS session, EEG sleep spindles were monitor online to observe the drowsiness level of the subjects at any given time. When the drowsiness level increase, the stimulation would be manually delivered.

6.2.3 EEG acquisition and analysis

EEG data was acquired using an ANT amplifier (Advanced Neuro Technology, Enschede, Netherlands) connected to 64 electrodes cap (Waveguard EEG cap, ANT). The electrodes were mounted on the cap based on the extended International 10-20 electrode placement system. All channels were referenced to the link of the left and right mastoids, and grounded with channel AFz. Input impedances of all channels were kept below 10kΩ for all experimental sessions. Data was sampled at 250Hz and recorded using ASA-lab software from Advanced Neuro Technology. For online EEG recording, ANT software development kit and Matlab 7.0 (Mathworks,USA) were used to capture each 5s data of EEG. This epoch would be preprocessed and analyzed to see if there is any spindle available.

Automatic artifact removal (AR) is performed to remove noises, electromyography (EMG) and electrooculography (EOG) artifacts from the raw signals (Kaiquan et al., 2013). EEG signals from 4 channels Fz, Cz, Pz and Oz were then extracted and processed to obtain spindle activity since the medial areas of the brain exhibited robust spindles detection with densities comparable to those observed in depth EEG (Andrillon et al., 2011). Spindles were detected automatically following previously published algorithms (Clemens et al., 2007; Ferrarelli et al., 2007). EEG spindles were selected based on two criteria: power and duration. EEG signals were bandpass filtered between 9 and 16 Hz (-3 dB at 8.8 and 17.3 Hz) using a zero-phase fourth order Butterworth filter. Hilbert transform was used to compute the instantaneous amplitude of and two thresholds were defined based on this amplitude time course across artifact-free EEG epochs. Potential spindles should have amplitude exceed a detection threshold set at mean + 3 SDs. A start/end threshold was set at mean + 1 SD and events whose duration was between 0.5 and 2 s were further considered. Detections within 1s were merged as single events. Next, only events in which power increases were specific to the spindle frequency range (11Hz-16Hz) were chosen for final analysis. For analysis of detected spindles, time-frequency map were computed in ± 1 s intervals around peak spindle power, using a short-time Fourier transform with a window of 744 ms and 95% overlap.

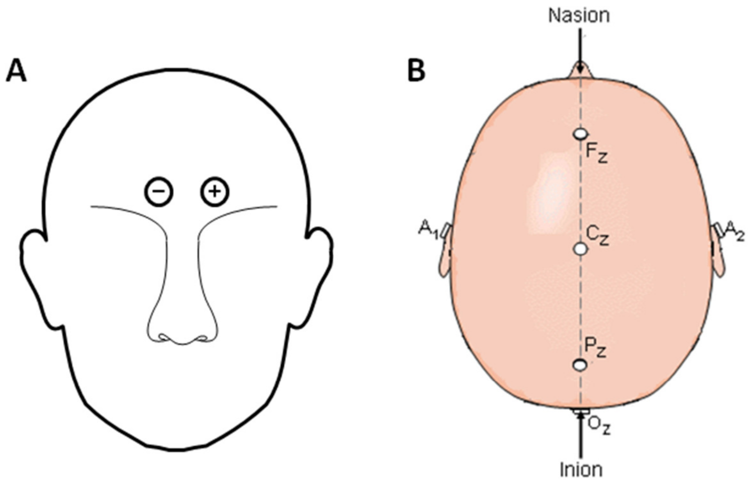


Fig. 6.2 Experimental setup: A. Stimulation electrodes were attached on subject's forehead to stimulate V_1 branches of trigeminal nerve; B. Spindle activity was obtained from 4 channels Fz, Cz, Pz, Oz since the medial areas of the brain exhibited robust spindles detection with densities comparable to those observed in depth EEG

6.2.4 Trigeminal Nerve Stimulation

An external pulse generator (Sapphire II, Tecca Medelec, USA) was utilized to deliver TNS at multiple parameter settings. The electrodes (3M^{TM} Red Dot electrode, USA) were placed on the forehead of the subjects to stimulate V_1 branches of the trigeminal nerve bilaterally (Fig. 6.2A). When increased drowsiness level was observed, the stimulation would be delivered for 100s, after that the stimulation was off until spindles appeared again. Current was randomly set at 2mA, 3mA and 5mA to investigate the effect of current. Pulse duration was 200µs, frequency was 70Hz.

To examine the effects of frequency, current were set at 3mA, pulse duration was 200µs, and the stimuli were delivered randomly in 2 modes: continuous mode at 70Hz or burst mode at 20Hz (Fig 6.3).

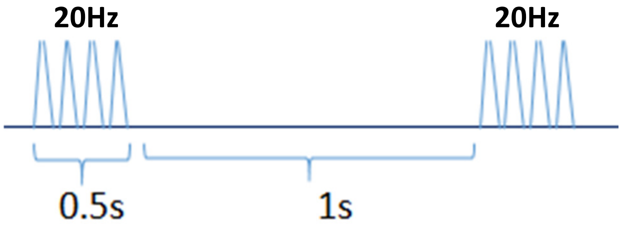


Fig. 6.3. Burst release mode of the TNS. Each burst of stimuli were delivered at 20Hz for 0.5s, the interval between bursts was 1s.

6.2.5 Vibration stimulation

Since participants could perceive the stimulation as a small vibration on the forehead, a forehead vibrator was used to investigate the effect of mechanical vibration on drowsiness. Two 1.5V cellphone motors attached on rubber pads were used. These pads had similar size to the TNS electrodes and were put on the same locations. Vibration intensity was adjusted to same level as the vibration created by electrical stimulation at 3mA and 5mA.

6.3 Results

6.3.1 Behavioral results

For control group, most of the subjects experienced micro-sleep during the task, average time spent before falling asleep was 32±7 minutes. The behavioral results showed that the prolonged time on PVT led to the increase of reaction time (Fig. 6.4A), reaction time of last 5 minutes before the micro sleep (RT = 509.94 ± 128.36 ms) was significantly higher than first 5 minutes (RT = 285.35 ± 79.69 ms), $p<0.01$. On the other hand, most of participants in the TNS group could last till the end of the experiment. No significant change could be detected in the reaction time of this group (Fig. 6.4D). The stimulation was perceptible at comfortable level and did not cause distraction to the subjects. The participants also reported that they felt more alert and more agile during the stimulation.

6.3.2 Spindles and performance deficits

Spindles did not appear at the first 5 minutes, but occasionally occurred when the participants felt tired and increased significantly right before the onset of micro-sleep (Fig. 6.4B), 4.23±1.24 at last five minutes before the micro-sleep, $p<0.0001$. Fig. 6.5 showed the EEG signals at the 4 channels and time-frequency map of Cz around 63s before and 27s after the micro-sleep. As can be seen, the abundant occurrences of spindles reflected the accumulation of sleep pressure, resulting in the micro sleep at 2023th second. The occurrence of these spindles was consistent between subjects and linearly correlated to the reaction time ($r = 0.78$, $p<0.001$) (Fig. 6.4C), increase of spindle rate comes along with slower reaction.

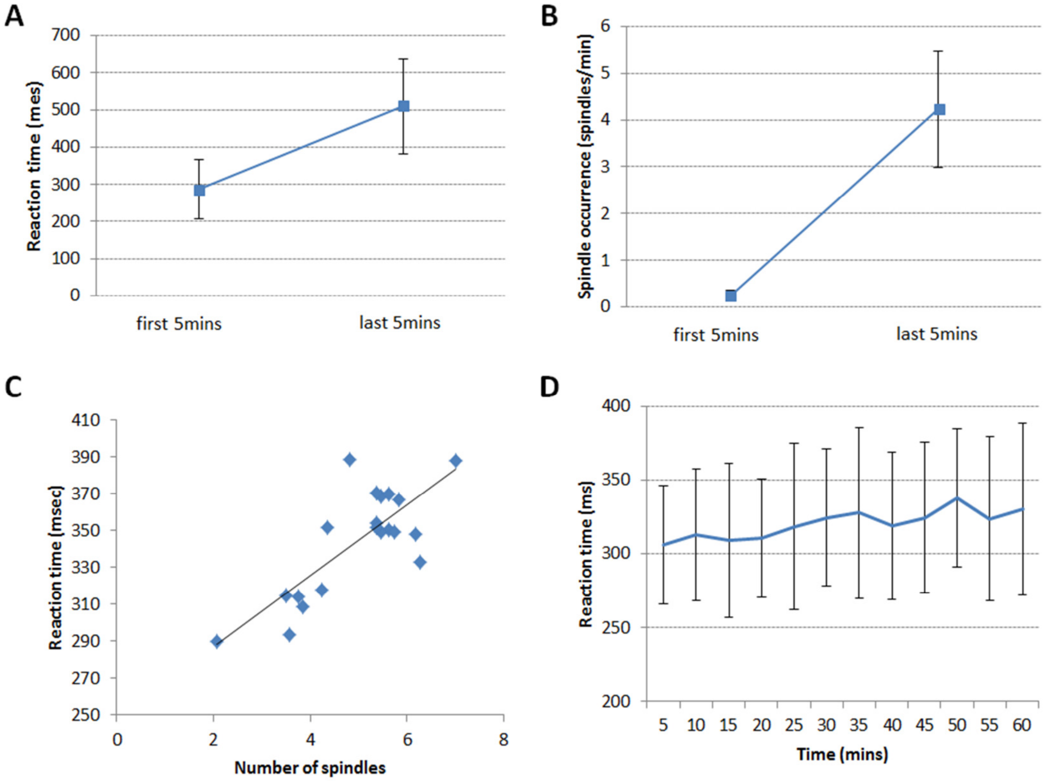


Fig. 6.4. A. Means and standard deviations of reaction time (RT) of control group at the first 5 minutes and the last 5 minutes before the micro-sleep; B. Number of spindles were detected at the first 5 minutes and the last 5 minutes before the micro-sleep from control group data; C. Significant correlation between RT and spindle rates ($r = 0.78$, $p<0.001$); D. Means and standard deviations of reaction time (RT) of TNS group across 60 minutes PVT.

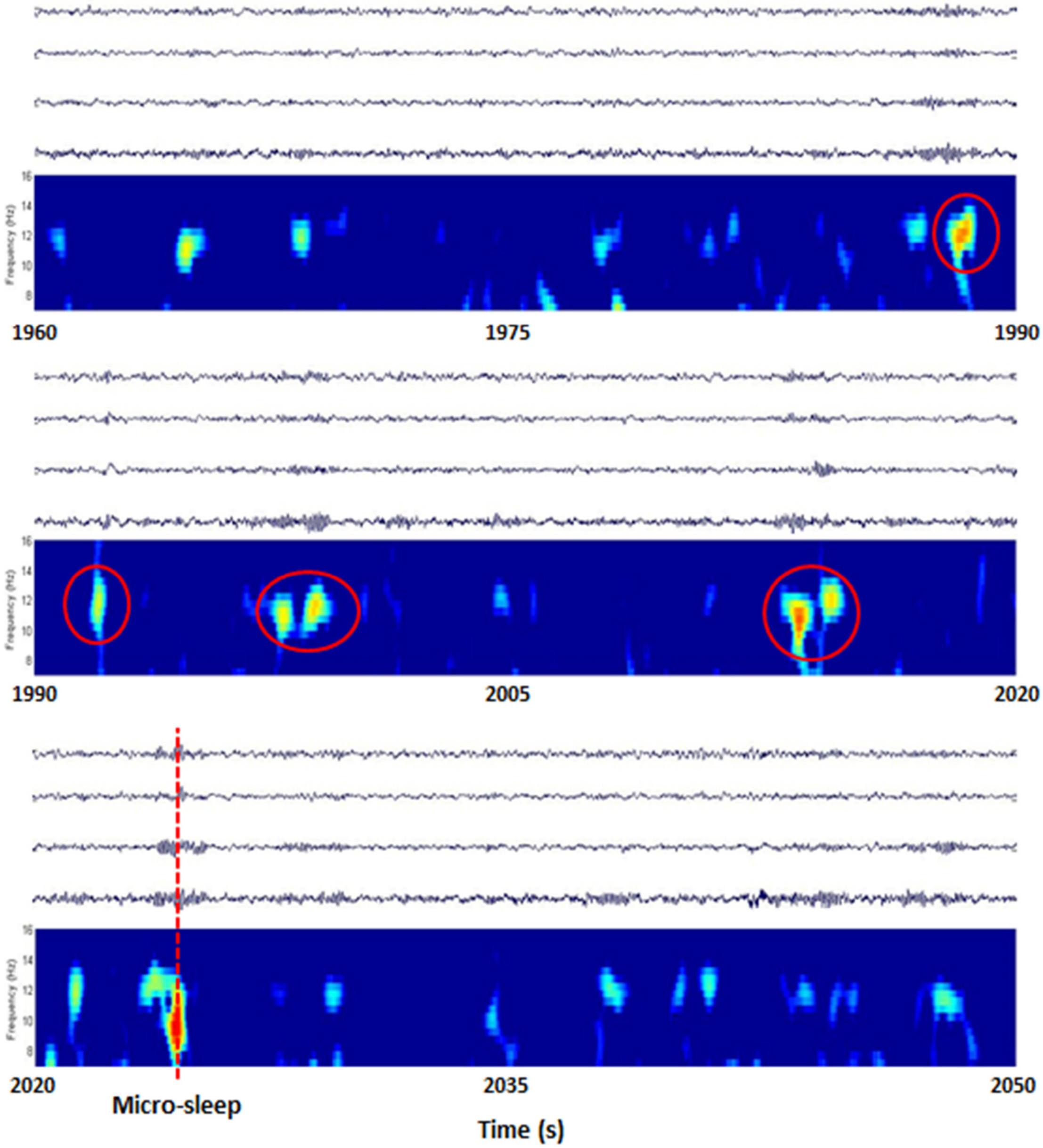


Fig. 6.5. EGG signal of Fz, Cz, Pz, Oz and time-frequency map of Cz during 63s before and 27s after the microsleep. Spindles were marked by red circle. Spindles, as an indicator of drowsiness, abundantly occurred before the onset of microsleep.

6.3.3 Effect of trigeminal nerve stimulation

As shown in Fig. 6.6, the spindles were suppressed after the onset of TNS, although the efficacy seems to be dependent on the current and frequency of the stimuli.

Effect of current

When current was set at 5mA, the effect of trigeminal stimulation could be observed nearly immediately, and this effect can last for next 200 seconds. While at 3mA, the influence of TNS was not as strong. It took longer time to suppress the spindles, and the spindles reappeared early after the stimulation was off (Fig. 6.7). At 2mA, the stimulation was not very effective. Although spindle occurrences did decrease under stimulation, it was still there and quickly increased after the end the stimulation.

Effect of frequency

The stimulation delivered in burst mode appears to be more effective than the continuous mode. Right after the onset of stimulation, the spindles were suppressed and the effect still lasted for more than 100s after the end of the stimulation (Fig. 6.8). At this setting, the vibration cause by the trigeminal stimuli was less perceivable, the subjects reported better tolerance.

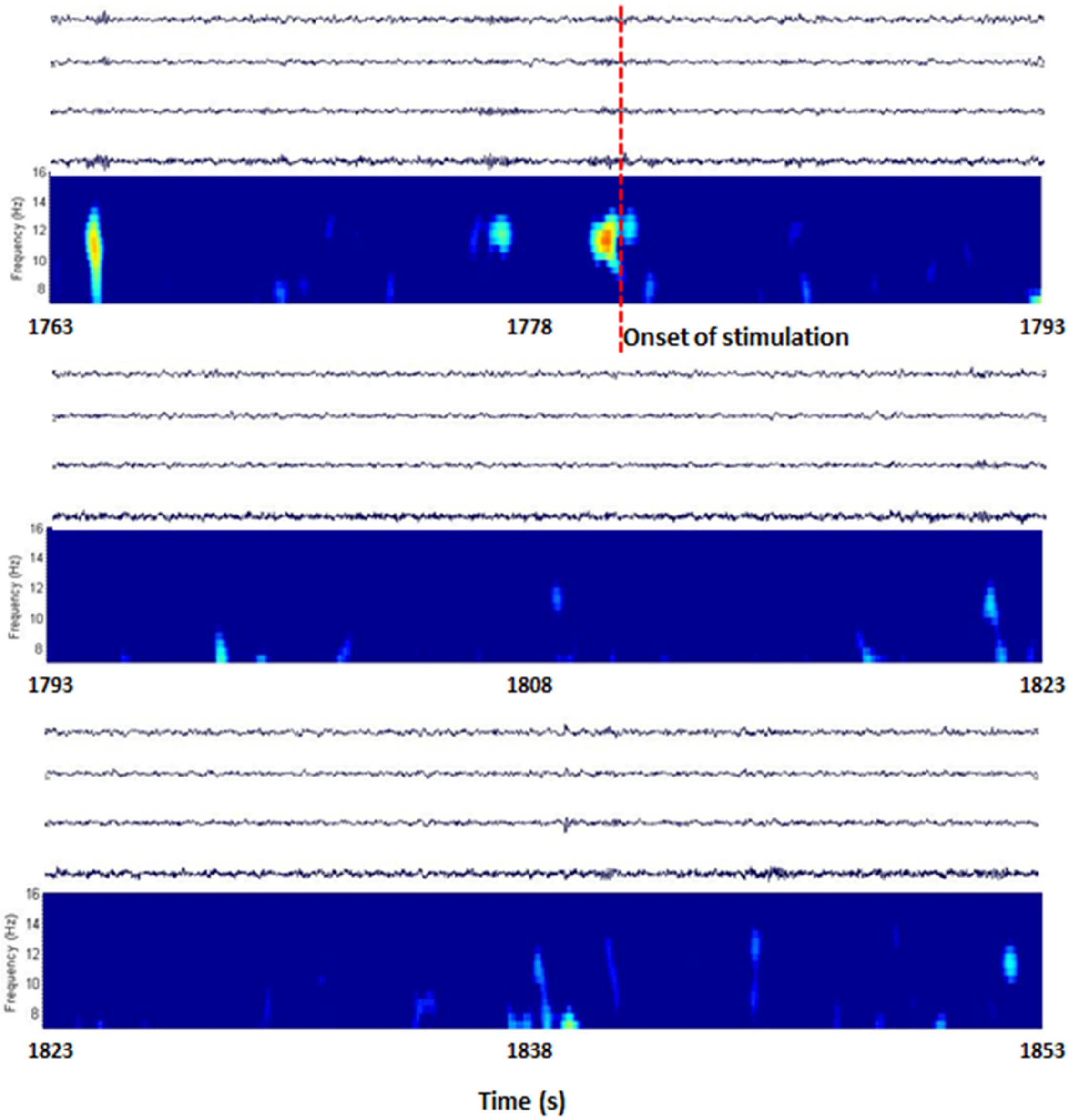


Fig. 6.6. EGG signal of Fz, Cz, Pz, Oz and time-frequency map of Cz before and after the trigeminal nerve stimulation. The onset of stimulation was marked by a red dash line. Spindles were suppressed right after the onset of stimulation.

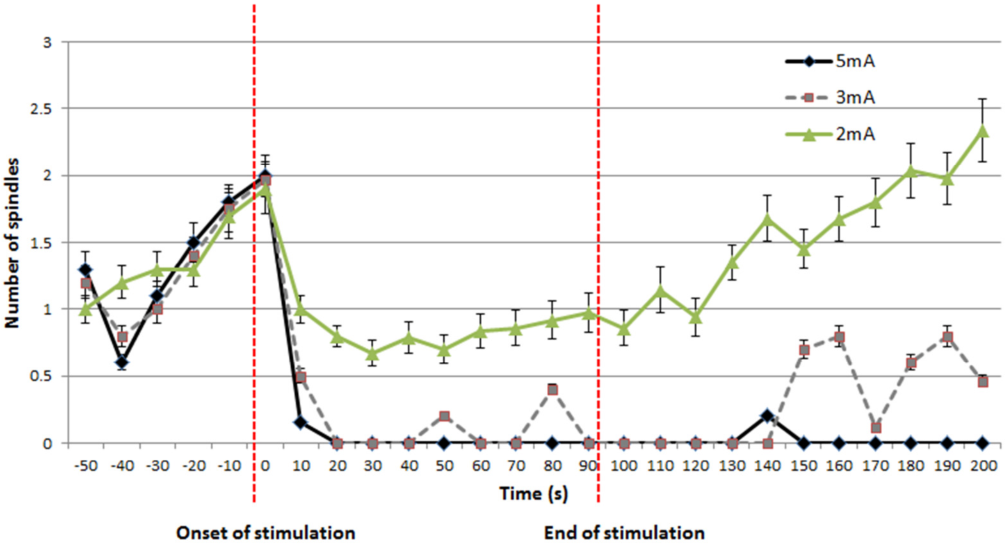


Fig. 6.7. Means ± SE of spindle rates before and after TNS at 2mA, 3mA and 5 mA current. The stimuli were delivered continuously at frequency 70Hz, pulse duration 200µs and last for 100s.

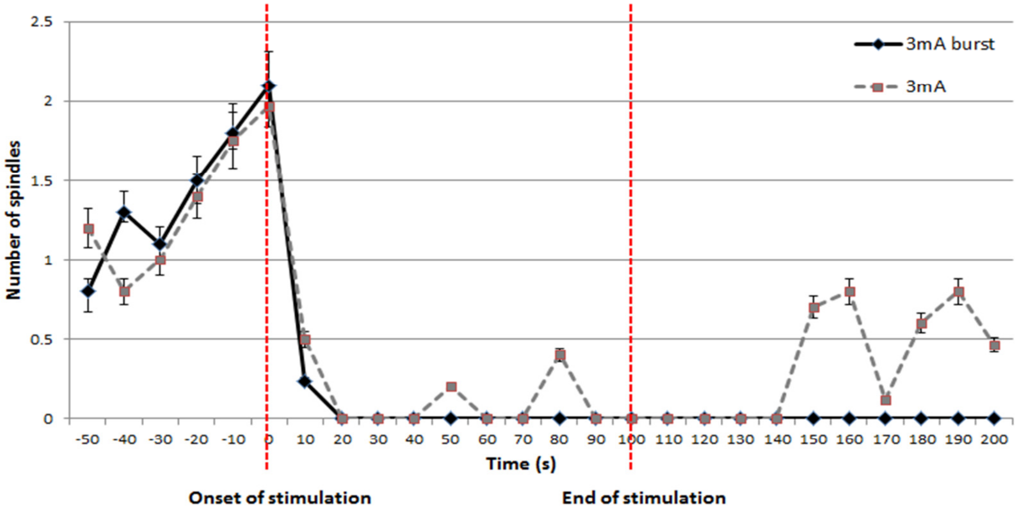


Fig. 6.8. Means ± SE of spindle rates before and after TNS at 3mA continuous mode (dash line) and 3 mA burst mode (solid line). Pulse duration was 200µs. The stimuli were delivered at frequency 70Hz in continuous mode and 20Hz in burst mode (on for 0.5s and off for 1s). All the stimulations were last for 100s.

6.3.4 Effect of mechanical vibration

As shown in Fig.6.9, vibration created by mechanical vibrator could not interrupt the development of drowsiness. Change in vibration intensity also did not make difference. Participants even reported that they felt more comfortable and easier to fall asleep under this condition. This result confirmed that the effects of TNS were caused by the transmission of electrical stimulation inside the brain, not by mechanical vibration.

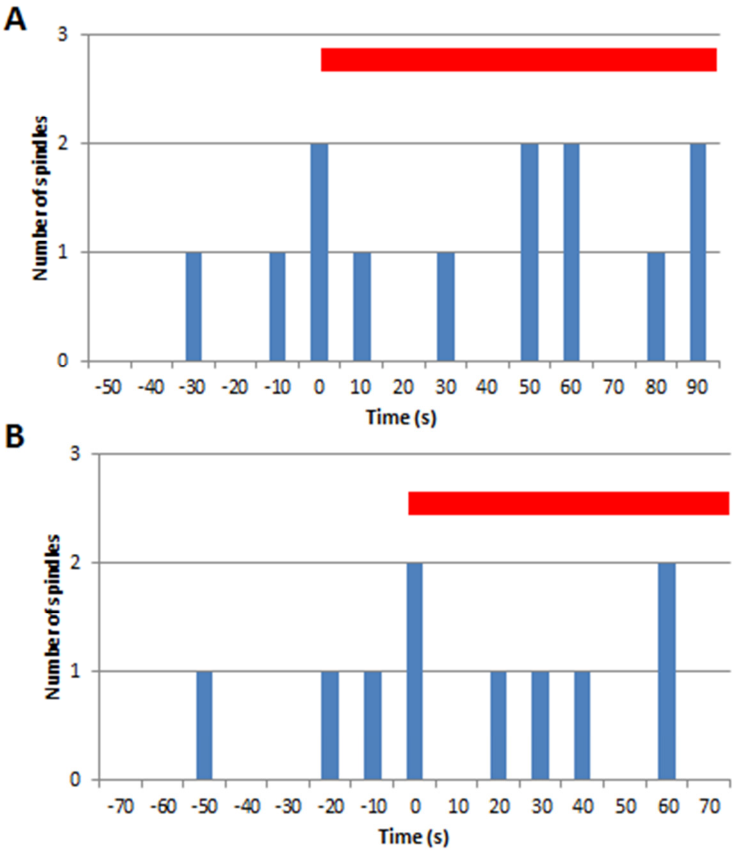


Fig. 6.9. No effect of mechanical vibration on drowsiness has been observed. Vibration intensity was adjusted to same level as the vibration created by TNS at (A) 3mA and (B) 5mA. The available of stimulation were marked by the horizontal solid bar.

6.4 Discussion

The primary finding of this study is that TNS could suppress the drowsiness and prevent unintentional sleep onset. The participants reported that the stimulation were comfortable and did not create any distraction. The effect of the TNS was confirmed by the suppression of EEG sleep spindles.

Literature has shown that spindles are generated by GABAergic neurons in thalamic reticular nucleus during ‘burst’ firing (Steriade, 2000). The thalamic reticular complex is a thin sheet of neurons surrounds the thalamus, contains only GABAergic cells and is considered as a controller of thalamus firing (Halassa et al., 2011). When the GABAergic cells are active, they will strongly inhibit relay cells in thalamus that these relay cells no longer fire action potentials in response to inputs from external environment or from cortical areas. Under these conditions, the thalamic gate is shut, leading to the loss of vigilance and alertness (Datta and Siwek, 2002). As be created by TRN during burst firing, spindles only appear during inattentive awake, drowsiness and early states of sleep. Their occurrence thus reflects the blockage of the communication between thalamus and cortex, ranging from sensory transmission, to cortical plasticity and learning (reviewed in Lüthi, 2013; Steriade, 2001b). Hence, the correlation between spindle occurrences and performance deficits found in this study was expected and reasonable.

The effect of the stimulation could be explained by the pathway of trigeminal nerve. Since trigeminal nerve can convey the signal to cerebral cortex and deep brain areas such as ACC and LC, the stimulation excites neurons in these structures, resulting in the increase of neural modulator inputs such as dopamine, noradrenaline to the cerebral cortex. The increasing activity of these projections disinhibits thalamus relay cell, thereby opening the thalamus gate, and enhances activation in the cortex. As a result, the spindles will be suppressed together with the drowsiness. Furthermore, increase activity in ACC and LC could lead to better behavior adjustment (Ide et al., 2013), explaining the subjective reports that they felt more agile during the stimulation.

It is well documented that the stimulus with high current could excite more neurons than low current one. Since axons are the main element activated by electrical stimulation, higher current could activate more cells through the dendrite of neurons (Histed et al., 2009) and make the stimulation more effective. This could explain differences in the effectiveness of the stimulation at 2mA, 3mA and 5mA in the results. Similar trend has been observed from previous studies (Fanselow et al., 2000), where increase current leads to significant improvement in promoting wakefulness.

The firing rate of LC could be the reason behind the differences between continuous stimulation and stimulation in burst mode. A significant characteristic of LC neurons is their slow, tonic discharge pattern. LC neurons alter their tonic impulse activity in association with changes in vigilance. According to animal studies, highest tonic LC discharge rates (around 6Hz) occurred with exploratory alertness; lower tonic activity (1Hz-2Hz) occurred during quite wake and grooming, and LC activity was dramatically diminished before the onset of the drowsy state. In addition to these changes in tonic activity, LC neurons were also phasically responsive (release a burst of spikes in a short time) to certain sensory stimuli like auditory, visual, or tactile stimuli. Hence, it seems to be feasible to wake LC by mimicking the response of LC to sensory stimuli, delivering a burst of electrical stimuli each few seconds. The result in this study is similar to the literature (Devoto et al., 2005). In this paper, the authors showed that the stimulation with bursts of pulses at 12Hz and 24Hz each 1s or 2s increased not only noradrenaline but also dopamine levels.

Although the preliminary results are promising, there are many remain to be studied such as the effects of frequency, duration of pulse as well as the differences in gender, age, and how long the effect of stimulation can last. Hence, additional larger trials are needed to delineate efficacy and tolerability with greater reliability.

6.5 Concluding Remarks

The study had provided evidences of unintentional sleep onset intervention by trigeminal nerve stimulation. The effects of the stimulation were supported by the suppression of spindle activity, which is associated with increasing vigilance and alertness. The appeal of this approach is that it is a non-invasive technique. The forehead stimuli were well-tolerated and could be used to suppress drowsiness for a long time, which is critical in certain real life situations.

Chapter 7

Conclusions and Recommendations for Future Work

7.1 Conclusions

This work provided an essential step toward the development of a system that can provide reliable and early feedback on individual's fatigue level at any given time and deliver stimulation to quickly suppress the fatigue effects. The system can essentially contribute to the prevention of fatigue related accidents, which has become more inevitably common nowadays.

Firstly, a neurophysiological indicator of mental fatigue, the EEG spindles, was determined and served as the foundation for the proposed system. This indicator was first suggested by the increase in activation of thalamus along with the decreased activity of cortex areas such as frontal and parietal cortices, anterior cingulate gyrus, precuneus, medial frontal cortex and cerebellum. Then the connectivity analysis revealed the disruption in the functional connectivity between thalamus and these regions under fatigue as a result of the increase of spindle occurrence, proving the correlation between spindles and mental fatigue. The validity of spindles as an indicator of mental fatigue was examined in various tasks: number sequence discrimination task, psychomotor vigilance task and simulated driving task for different cognitive function. All the results showed a consistent correlation between spindles and the performance deficits.

Secondly, the spindle-based fatigue detection was showed to be more reliable and flexible than the well-known traditional approach based on visual behavior. Additionally, the results revealed that spindles can reflect the effects of both work-induced fatigue and circadian fatigue. Altogether, it is safe to say that EEG spindle is a direct and reliable indicator of mental fatigue.

Another significant contribution of this study is the development of a novel mental fatigue intervention approach, trigeminal nerve stimulation. The approach utilized a crucial characteristic of trigeminal nerve: it can convey electrical signals to important structures in the brain, including the anterior cingulate cortex (ACC), the thalamus and the locus coeruleus through the trigerminal nerve branches. The results showed that trigeminal nerve stimulation can quickly suppress spindle activity and improve individual performance and alertness. Compared to other fatigue intervention methods such as the use stimulated music, blue-enrich white light, which may need hours or days to see the effects, this novel approach is faster since it direct stimulates the wake-promoting area locus coeruleus and the behavioral adjustment network ACC-thalamus-locus coeruleus. Additionally, the method also has practical advantages: non-invasive, affordable, could be portable and easily apply to real life.

Besides, this study provided more understanding about mental fatigue. The functional imaging results showed the effects of mental fatigue on the brain activation and the trend of change of activation in susceptible regions along with the increase of mental fatigue. The decrease of activation in these regions could explain for the loss of vigilance, attention and dysfunction in cognitive processing often found in fatigued people. Moreover, the functional connectivity results revealed that mental fatigue not only causes dysfunction in cortex areas, but also cause disruption in the thalamic connectivity. The functional disruption of the thalamic connectivity to the cortex under mental fatigue supports the hypothesis proposed by Theyel (Theyel et al., 2010) that the thalamocortical connections not only relay sensory information but also have crucial role in higher-order cognitive functions via the transthalamic pathway, providing a new view on the role of thalamus in regulating mental states.

7.2 Recommendations for Future Work

Although promising results about mental fatigue detection and intervention have been showed and evaluated, it should be interpreted in light of several limitations. Firstly, due to the limitations of fMRI and EEG, the present study could only give a view on the association of mental fatigue to thalamocortical connections at functional imaging level. A cellular level investigation could deepen our knowledge on the neural mechanisms of mental fatigue and answer how it affects neurons firing, the role of thalamus to fatigue and especially the role of transthalamic pathway in regulating mental states.

Secondly, the age of the subjects is from 19 to 25, hence the effects of aging have not been investigated. Literature has shown that there are some differences in the brain connectivity of elder compared to young people, these differences may make older people more prone to mental fatigue. Aging also induces multiple changes to sleep spindle (Martin et al., 2013), including lower spindle density, amplitude, and duration. Hence, it is interesting to see if aging causes alteration in thalamic connectivity or not.

Additionally, more study on the parameter of trigeminal stimulation is needed. Although the preliminary results were promising, there are many remain to be studied such as the effect of frequency, duration of pulse as well as the differences in gender, age, and how long the effect of stimulation can last. Hence, additional larger trials are needed to delineate efficacy and tolerability with greater reliability.

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