STUDY OF CIRCADIAN MENTAL FATIGUE BY fMRI

ZHOU WEI
(*B. ENG, NUS*)

A THESIS SUBMITTED
FOR THE DEGREE OF MASTER OF SCIENCE
GRADUATE PROGRAM OF BIOENGINEERING
NATIONAL UNIVERSITY OF SINGAPORE
2006

ACKNOWLEDGEMENT

First of all, I would like to express my sincere appreciation to my supervisor, Associate Professor Li Xiaoping for his gracious guidance, a global view of research, strong encouragement and detailed recommendations throughout the course of this research. His patience, encouragement and support always gave me great motivation and confidence in conquering the difficulties encountered in the study. His kindness will always be gratefully remembered.

I would also like to thank Associate Professor E.P.V. Wilder-Smith, from the Department of Medicine and Associate Professor Shue Fwushan, from the Department of Biology Science, and Associate Professor Steven Graham from Department of Psychology for their advice and kind help to this research.

I am also thankful to my colleagues, Mr. Cao Cheng, Mr. Fan Jie, Mr. Mervyn Yeo Vee Min, Mr. Ng Wu Chun, Mr. Ning Ning, Miss Pang Yuanyuan, Mr. Seet Hang Li, Mr. Shen Kaiquan, Mr. Zheng Hui, , and Mr. Zhan Liang for their kind help, support and encouragement to my work. The warm and friendly environment they created in the lab made my study in NUS an enjoyable and memorable experience. I am also grateful to Lee Wei Wei who is the cooperator in the project, and also Dr. Liu Kui, Dr. Qian Xinbo, Dr. Zhao Zhenjie and Mr Soon Chun Siong for their kind support to my study and work.

I would like to express my sincere thanks to the National University of Singapore and the Graduate Program of Bioengineering for providing me with this great opportunity and resource to conduct this research work.

Finally, I wish to express my deep gratitude to my parents, my brother and my husband for their endless love and support. This thesis is dedicated to my parents.

TABLE OF CONTENTS

SUMMARY

In recent years, there is an increasing interest in fatigue-tracking technologies with the widespread hope that they will be invaluable in the prevention of fatigue-related accidents. In the literature, various efforts have been put into the fatigue measurement methods, including performance, perceptual, and electrophysiological based measurements. Majority of previously published research findings on fatigue have found varying results, which could be due to methodological limitation. However, there are fewer studies on the neural firing state across the whole process of fatigue, induced by the circadian rhythm. It therefore needs further research to get conclusion regarding the neural activity of the fatigue brain.

Based on a number of previous studies, we proposed four hypotheses for the circadian fatigue progress by fMRI to indicate the neural firing states when the circadian fatigue is progressing. First, a decreased brain activity occurs throughout the whole circadian fatigue process; second, there are specific parts of the brain which are more sensitive to the circadian fatigue; third, ACC and TH effect of the circadian fatigue; fourth, the auxiliary brain regions searched following the circadian fatigue progresses.

This study presents the usage of fMRI method to find out the neural activity of the brain under the different fatigue states, based on an auditory discrimination task. Results from the present study show that the circadian mental fatigue causes over all brain activity decrease. The brain protects compensate for these effects of circadian fatigue by manipulating the activation status of the areas in PFC, AFC, PL, ACC and TH. In the AFC, a sensitive decreased activation was observed across four sessions. For the PL, on the other hand, an equivalent activity was observed in the superior PL as well as the inferior PL. The ACC and the TH were found to be more strongly

activated following the circadian fatigue extreme. The DLPFC, which mediates both attention and arousal after fatigue, in order to maintain intact performance, also showed continued decrease in activity as a consequence. The precuneus, and the insular cortex which are not designed to be the ROIs were two other areas found to be involved in the circadian fatigue.

Finally, this fMRI based study provides a better understanding of the anatomical characteristics of the mystery of the brain in circadian fatigue, but also helps in the development of fatigue counterwork using a combined technique of EEG and fMRI.

LIST OF TABLES

LIST OF FIGURES

LIST OF NOTATIONS

AC	Anterior Commissure
ACC	Cinguli Gyrus
AFC	Anterior Frontal Cortex
ADT	Auditory Discrimination Task
Au	Auditory Cortex
BA	Brodmann Area
BOLD fMRI	Blood Oxygenation Level Dependent fMRI
DLPFC	Dorsolateral PFC
ECG	Electrocardiogram
EEG	Electroencelphalogram
EMG	Electromyogram
ESS	Epworth Sleepiness Score
fMRI	Functional Magnetic Resonance Imaging
GFc	Gyrus Frontalis medialis
GFi	Gyrus Frontalis inferior
GFs	Gyrus Frontalis superior
GLM	General Linear Model
GPoC	Gyrus Postcentralis
GPrC	Gyrus Precentrallis
GTi	Gyrus Temporalis inferior
GTm	Gyrus Temporalis medius
GTs	Gyrus Temporalis superior
GTT	Gyri Temporales Transverse
Hi	Hippocampus
INS	Insula
LPi	Lobulus Parietalis inferior
LPs	Lobulus Parietalis superior
MEG	Magnetoencelphalograph
Mo	Motor Cortex
NIRS	Near Infrared Spectroscopy
NSD	Number Sequence Discrimination
PC	Posterior Commissure
PCu	Precuneus
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PL	Parietal Lobe
ROI	Region of Interests
RT	Reaction Time
SMA	Supplemental Motor Area
SSS	Stanford Sleepiness Scale
TH	Thalamus

TL	Temporal Lobe
TTD	Target Tone Discrimination
VLPFC	Ventrolateral PFC
WM	Working Memory
β	The parameter estimate for the model in the GLM

1 Introduction

1.1 Background

Mental fatigue is a common feeling of thousands of people during their work everyday. Seriously, there are hundreds of thousands of accidents in our industrial world due to the fatigue of operators. From several wrong arithmetic problems on the small papers of the primary school students after a long exam to the amazing number of the traffic accidents due to the fault of the mental operation, fatigue is a big threat to our life every day. According to the early work by Idogawa (1991) on driver fatigue, it is believed to account for 35-45% of road accidents. Recently, an estimation made by the National Highway Traffic Safety Administration in the United States has announced the figure of road accidents reported due to fatigue related drowsy driving to be 100,000, resulting in 1,500 fatalities each year (Stutts, Wilkins, & Vaughn, 1999). However, what is mental fatigue? How does our brain experience such common but unraveled mental mystery?

A lot of efforts have been focusing on it since people realized the mental fatigue is such a big threat to them. Interest in fatigue may have been demonstrated a long time ago but actual documentation dates as far back as World War I. Research in fatigue has since that time passed through different eras of interest. However, only two of these including the third which is still ongoing are of consequence.

The first era of interest on the phenomena of fatigue was in England during the First World War and the research at this time was conducted by the Industrial Research Fatigue Board. The major focus on the work of the Board was understandably in the munitions industry. The primary concern was the effect of fatigue on productivity. It was postulated that fatigue effects were as a result of work (daily or weekly), shift changes, illumination and ventilation, work place design, and plant layout the criteria used to measure fatigue was total out put of manufactured items and hence and ensuing reduction in output was ascribed to fatigue (Cameron, 1973).

The next major surge in interest was demonstrated in the period immediately preceding, and towards the end of the Second World War. A major research effort at this time focused on military and civilian aviation. A major work of this era was conducted by Viteles (1946) and members of his committee for the U.S. Civil Aeronautics Administration. The focus of much of their work was the attempt to establish appropriate standards of operation of aircrafts to avoid excess fatigue. Their report concluded that performance effects alone were not and should not be the exclusive area of interest in describing fatigue. Two researchers during the same period (Eartly and Chute, 1947) supported this view by emphasizing the complex nature of fatigue and went further to distinguish three distinct facets of the problem of fatigue. These three categories were: 1. the subjective feeling; 2. Impairment as a reduction in physical capacity due to accumulated oxygen debt in the muscles and finally; 3. work decrement as exteriorization in performance for reasons other than sheer physical incapacity.

The third era of interest in fatigue had an early beginning, but real interest was developed in the early fifties and is still very active at the present time. The research was focused on two different but related areas. The first is the area of fatigue during driving and the effects on accident rate. A major research in this area was spearheaded by Brown (1967). Most of the work on fatigue in driving implies that safety is the ultimate goal and so the number of accidents is used as the criterion. Another area that has generated considerable interest is the area of fatigue and Air Trafific Controllers (ATC) and the resultant health change (Rose, 1978). In this area the emphasis is on the chronic and cumulative effects of fatigue and a concern with the long-term wellbeing of the individual workers, i.e., traffic controllers. While it has not been proven that fatigue on the part of ATC leads to accidents, it has been recognized that the long-term effects on health and on the job satisfaction of ATC crews are legitimate areas of concern.

Most of the investigations up till now were concerned with fatigue as it affects physical and paraphysical work. Very little has been reported with regard to the phenomena of fatigue during activities which are mostly mental.

1.2 Problem statement

Fatigue was believed to be a nonlinear, temporally dynamic, and complex process which results from the various combinations of many factors, sleep loss, extended work periods, circadian rhythm, and etc (Dinges, 1995). Fatigue can refer to a subjective symptom of malaise and aversion to activity or to objectively impaired performance. It has both physical and mental aspects. The physiological and psychological mechanisms underlying subjective fatigue are poorly understood. One

common definition of fatigue in medicine is that fatigue is the "state following a period of mental or bodily activity characterized by a lessened capacity for work". The concept of mental fatigue early introduced by Grandjean (1981), clearly differentiated mental fatigue from physical fatigue. He defined that physical fatigue is concerned on the reduced muscular system performance; mental fatigue deals with much reduced mental performance, and the sense of weariness. Cortical deactivation occurred during fatigue has been reported by recent researches on driver fatigue (Brookhius & Waard, 1993; Kecklund & Åkerstedt, 1993; Waard & Brookhius, 1991). In this study, only mental fatigue was investigated for its increasing influence on operation safety and work efficiency (the word "fatigue" refers to mental fatigue hereafter in this study).

The complexity of fatigue metric makes it difficult to be detected or identified. Though the increasing number of fatigue detection technologies comes out, such as the ECG, EMG, EEG, heart rate and respiration, there is still no clear understanding of the fatigue mechanism in our brains. Previous studies have shown that the link between each parameter changes and fatigue levels depended on task design, subject state, and the psychological states. These studies differ from the precise nature of their fatigue-detection algorithm to the number and the equipment limitations from which they record (Makeig & Jung, 1995; Lal & Craig, 2002). Therefore, a further study of the fatigue mechanism is needed and the understanding of the neuronal activity in the brain during the whole process of the circadian mental fatigue progress is critical. After the technique of fMRI has been developed with high resolution of the indication of the brain, it becomes the most promising method to detect the fatigue. Furthermore,

for the future understanding of the fatigue, study of the fatigue combined with the EEG and the fMRI is most prospering methods.

1.3 Research objective

The apparent evidence shows that a clear relationship between circadian fatigue and the cognition is in place since circadian fatigue results in an impaired performance in cognitive tasks. In view of this, as well as the many studies linking the circadian fatigue to the proper functioning of the central nervous system, the current study seeks to investigate the effect of circadian fatigue on the brain activity during a 24-hour sleep deprivation. A number sequence discrimination task was administered to the subject during fMRI* scanning. Subjects were required to maintain 'on-line' the present stimulus and subsequently make a response according to the number sequence. Individual analyses were performed for the region of interests (ROIs): Dorsolateral prefrontal cortex (DLPFC), Ventralateral prefrontal cortex (VLPFC), anterior frontal cortex (AFC), Parietal lobe (PL), primary motor cortex (Mo), Temporal lobe (TL), Cinguli gyrus (ACC) and Thalamus (TH). ROIs were defined by a combination of functional activation and anatomical landmarks. This approach considered activated voxels within the anatomically defined ROI without including areas that lay in the ROI but were not activated above threshold.

The following hypotheses were tested:

The 1st hypothesis: the circadian fatigue will cause general decreased activity of the brain which should be coherent with the decreased performance.

* fMRI: functional magnetic resonance imaging

The 2nd hypothesis: there should be some specific parts of the brain which are sensitive to the circadian fatigue.

1. Based on the auditory task, when the circadian fatigue progresses, the prefrontal cortex (PFC) of the brain will decrease its activity in advance compared to other areas which are also concerned with the task, e.g. the auditory cortex and the primary motor cortex. In other words, the frontal cortex shows much more sensitive characteristics than others. The prefrontal cortex (PFC) comprised 3 areas, namely the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and the anterior frontal cortex (AFC). We aimed to find out their sensitivities to the circadian fatigue.
2. Activity in prefrontal cortex (PFC) and parietal lobe (PL) was reduced following the circadian fatigue. Although the study (Drummond et al. 1999) was employing a working memory paradigm, the same trend was postulated.

The 3rd hypothesis is that accompanying the circadian fatigue, a greater fMRI signal would be found in the cinguli gyrus (ACC) and thalamus (TH). The cinguli gyrus (ACC) has been implicated in mediating arousal (Jansma et al., 2000), while the thalamus (TH) has been found to be involved in mediating attention (Portas et al., 1998). Since sleep deficit results in reduced vigilance (Binks et al., 1999) and lowered arousal (McCarthy & Waters, 1997), the subjects would need to counteract these physiological responses by compelling themselves to not only stay awake, but also complete the task. In the task all subjects were informed before-hand that payment would only be administered following the successful completion of the task. As such, the monetary motivation to stay awake would result in increased activation in cinguli gyrus (ACC) and thalamus (TH).

The 4th hypothesis is that circadian fatigue results in recruitment of auxiliary brain regions during the performance of the task. Following the reduction in signal in the prefrontal cortex (PFC) (Drummond et al., 1999), it is likely that additional brain areas will be recruited so as to compensate for the effects brought about by the decreased activity of the prefrontal cortex (PFC).

2 Literature Review

2.1 Circadian fatigue

The body's processes have peaks and valleys during every 24-hour period. These are called circadian rhythms. Time cues – such as sunlight and work/rest schedules keep the circadian clock set. Crossing time zones or changing form a day shift to a night shift forces the circadian clock to move to a different schedule. Disruption of the circadian rhythm when combined with loss of sleep can create a dangerous increase in fatigue.

Research in the past thirty years, has indicated that people are diurnal and that performance and sleepiness responds to a circadian 24 hr clock (Tepas 1994). Research has consistently found that an increase in sleepiness and a related decrease in performance occur at two particular periods of the day, during the night at the time of normal sleep and in the early afternoon. It is during these two periods that human functioning is at its lowest point. Perhaps the effects of time of day can be most readily seen by the examination of accident data. Research has consistently shown that time of day is an important factor in accidents (McDonald, 1984; Haworth, Hefferman & Horne 1989; Haworth & Rechnitzer 1993; Hartley & Arnold 1995; Lisper, Eriksonn, Fagerstrom & Lindholm 1979). Early work by Prokop & Prokop (1955 cited in McDonald 1984) indicated that drivers who had fallen asleep at the wheel tended to do so between the hours of 23:00 and 05:00 hours (58%) and between the hours of 12:00 and 15:00 hours.

The circadian rhythms are controlled by a biologic clock located in the suprachiasmatic nucleus of the hypothalamus. Many biologic systems, such as hormonal secretion, follow a circadian pattern. The generator of sleep which will cause the circadian fatigue is not known but may involve neurons in the preoptic-anterior hypothalamic region. The cycle of the sleep-wake is associated with state-specific activity of brainstem and thalamic neurons.

2.2. The brain and the mental process

An understanding of the physiological mechanisms used by the human brain for thinking must begin with anatomy, with the identification of what parts of the brain play what role in thought processes. The brain, also known as the cerebrum is a vast collection of neural cells connected by neuronal arc and synapses with a complex series of inter neurons between the limbs of the arcs (Gardner, 1975). Till now, the mechanism of the neural activation and deactivation mechanism has been going much further.

The brain is made up of the forebrain (prosencephalon), the midbrain (mesencephalon) and the hindbrain (Rhombencephalon) and is protected by three layers of non-nervous tissues which are collectively called the meninges. The outermost layer of this tissue is the dura-mater, the middle layer – the arachnoids and the innermost layer – the pia-mater (Gardner, 1975; Holloway, 1968) from observations of the areas of the brain that show evidence of increased work during thinking or other cognitive tasks, a model has been developed for those areas of the brain responsible for thinking and

memory. The model involves cortical structures of the cerebral hemisphere, with zones in the upper brain stem, the mediobasal portions of the temperal lobes and cortex, the thalamus, and the striopallidal system (Bechter-eva, 1981; Gogolitsin et al, 1981; Ojeman, 1981; Ojeman, 1968; Peterson et al, 1959). The cerebal maintenance of the functions of thinking and memory is due to linkage of the system evolving from the aforementioned areas, each area functionally complementing the other.

2.2.1. Human thought process

The human brain engages in, and is responsible for, among a host of other things, functions and specialization which are vital in intellectual and cognitive processes. Although the basic mechanisms of some of these cerebral functions cannot be ascertained, it has been established that these functions are critically dependent on certain areas of the brain namely the association areas.

The association areas are used to designate all those areas of the cerebral cortex to which actual physical function of associational areas to unite the external or physical world with the internal or bodily world (Berry, 1928). Most modern authorities (Gardner, 1975; Russell, 1975; Rosenblueth, 1969) regard the association areas as being responsible for the higher processes of reflection, intelligence and volition. As being the true instrument of speech and thought; as being the region in which the efferent sense impressions are synthesized into complex perceptions or concepts; and as being the area where memory record of past experience and their connections are laid down and stored in the cortical network of neurons.

The human thought process as part of the cerebral function is very difficult to define and in fact is not exactly alike in any two individuals. Thinking, in a broad sense, involves the linking and recalling of one memory with another and the forming of decisions for actions (Russell, 1975). Speech and thought depend on a charging of cortical neurons by suitable impulses intellectual differences between individuals are brought about first by the number of cortical neurons possessed and by the nature of the receptor impulses which charge of stimulate those neurons.

Memory and the thought process both depend primarily on the integrity of the cerebral cortex and thalamus on one hand and the limbic system on the other. The workings of these two systems even though separate are intertwined and complementary. While the brain is under the affect of the alerting system, innumerable repetitions of a visual pattern are made and this results in memory being formed. The limbic system provokes thought processes not only by encouraging the original visual pattern to be reactivated over and over again but also by encouraging the recall of similar related experience in the past. The stores of past information are not in the limbic system itself. These mechanisms of storage are in the cortical and thalamic areas of the cerebral hemispheres. The cortical mechanisms are responsible for the details of given information (visual, auditory, etc.) to be studied. Thus the cortex must guide or train limbic system to drive the cortex – in a pattern which the cortex itself must to a large extent determine (Russell, 1975).

2.2.2. Physiological correlates of mental fatigue

The fundamental property of a cell is excitability, the ability to respond or react to a stimulus, that is, to the application of some energy change. When any neuron is

stimulated by the stimulus to which it is designed to react, a change takes place in the neuron and dendron (Berry, 1928; Gardner, 1975; Rosenblueth, 1969; Russell, 1975). The nature of this change is unknown but it is believed to be chemical, physical, physico-chemical or even electrical (Hill, 1968; Gardner, 1975; Berry, 1928). These chemical or metabolic changes in the cell-body of the neuron and dendrites result in the release or consumption of nerve energy within the nervous system (Hill, 1968; Gardner, 1975). Any neuron which is subjected to some stimulus will in combination with other neurons discharge the resulting energy or impulse on to the next neuron.

In general, the cells of all tissues exhibit a balance between the process of consumption of material associated with their activities and process of repair. If the stimulation reaching the neuron is too strong or is repeated at too brief an interval, then the process of repair do not keep pace with those of consumption. The excessive activity in the neuron due to over stimulation results in temporary or permanent physico-chemical changes in the nerve cell due to the removal of chromation materials from the cell body of the neuron. The ensuing condition known as chromatolysis results in the phenomena of fatigue. If the adverse conditions persist and are extreme, the chromation material may become completely removed from the cell body of the neuron, a condition which leads to a functionally exhausted cell. If the cause of chromatolysis is not removed, in time the neuron will be destroyed and there will be a corresponding dimunition of nerve action (Berry, 1928). Mental activity in the course of intellectual process implies and expenditure of nervous energy through the consumption of the reserves stored up in the cells and replenished by nutritive contribution or the mobilization of reserves situated in other organs. Whether the reserves are exhausted, in which case the nervous elements can no longer

borrow from other tissues or whether chemical production of energy is rendered impossible. Mental functioning is greatly reduced or even abolished due to the lack of necessary energy. If the reserves are impoverished and poorly replenished or if the consumption of reserves be interfered with, cerebral activity will become difficult and irregular.

Pieron (1950) in an earlier work indicated that a slight difficulty in the energic processes would result in the most costly mental activities – the complex synthetic functions, constructive thought and efforts of attention being greatly curtailed or even impossible.

2.3. Cognitive activity of the brain influenced by the circadian fatigue

Fatigue may be with regard to less energy conservation (Berger & Philips 1995) and it was concluded that sleep was necessary for neuronal detoxification and restitution. Without normal rest – sleep, fatigue has also been found to play an important role in cognition deterioration. For example, Karni et al. (1994), and Gais et al. (2001) have demonstrated a circadian rhythm interfered fatigue improvement on a visual texture discrimination task. Similar studies by Stickgold (1998) et al. (2000a; 2000b; 2001) also demonstrated that circadian fatigue plays an essential adverse role in the consolidation of experience-dependent neuronal changes into a form that leads to improved task performance. Drummond et al. (2000) found that the circadian fatigue appeared to selectively impair cognitive tasks associated with a prefrontal cortex (PFC) focus. The current approach involved the administration of circadian fatigue and a subsequent assessment of how cognitive processing has been affected (Binks et al., 1999; Linde & Bergstorm, 1992; Harrison & Horne, 1997; Drummond et al., 1999;

2000). Of the many cognitive tasks involved, those pertaining to the verbal system have been most appealing, with studies focusing on the susceptibility of the verbal system to circadian fatigue being especially well replicated. According to Drummond et al. (2000), the decreases in specific cognitive functions observed after the circadian fatigue progressed are likely to be due to impairments in the cerebral systems which constitute the neural substrates of these functions. In conclusion, their findings posit that circadian fatigue assumes a crucial adverse role in the cognitive processing and consolidation of information.

Previous studies use many indicators to determine fatigue, including performance, perceptual, physiological, psychological based measurements (Lal & Craig, 2002). Among them, vigilance performance is preferred by many researchers (Hartley, 2000; Mallis, 1999). Rating scales or subjective estimates are unreliable which could not be relied on to determine fatigue (Dinges, 1989). The auditory reaction time task has been regarded as a promising criterion

Many tasks have been used to exploit the human cognitive activity. In reflection, the inner of the brain will be introduced to correspond to the stimulus. Therefore, the mechanism of the brain can be studied. The studies on the fatigue all share one common feature: they require the subject to respond to a particular stimulus and then record the response. The response may either be in frequency and accuracy of detections or in reaction times. The outside stimulus can be visual, auditory, or even sensorial. Here are some most common tasks, which have been introduced for investigating the vigilance, attention or inversely the fatigue.

2.3.1. Visual based task

Stroop test

Subject given a list of words belonging to either category: color stated matches that of word, color stated conflicts that of word. For example: Color matches word (Control) RED (with red color), GREEN (with green color), BLUE (with blue color); Color conflicts word (experimental): RED (with green color), GREEN (with blue color), BLUE (with red color). Subject is supposed to list the color of the word in both categories. Task assesses the interference response and measures attention indirectly. A lower reaction time would be expected with the responses generated from the second column as due to the interference effect.

Visual search task

The experiment involves the subject trying to identify a target among many distracters, of which the two have similar features. For example, the target may be a green circle, while the distracters will be green squares and blue circles. The subject thus has to search through all the items to quickly identify the location of the target. A response is required for both scenarios (either yes or no).

Visual discrimination task

The subject is showed a serial presentation of a 3 x 3 grid of colored letters. Each grid is displayed for 3 seconds. The subject is required to make a response by answering "yes" or "no" depending on whether he saw 2 same letters that differed in color. Task is reported to last 40 minutes (Belyavin, A & Wright, N. 1987).

The Multiple Vigilance Test

Subjects are required to discriminate between visual targets (usually letters) and standard stimuli (the same letter but rotated by 90º). Subjects have to answer as soon as possible. Task lasts about 30 min.

2.3.2. Auditory based task

Auditory Reaction-time Task

An acoustic stimulus is delivered every 20 s for 60 min to the subject through an output interface to headphones worn by the subject. The subject is required to respond to each stimulus as fast as possible by pushing a button (Conte, S. etc. 1995)

Wilkinson Auditory Vigilance Task (Assesses vigilance fluctuations)

An auditory discrimination task can be incorporated in which a target tone is interspersed with probe tones and played to the subject at regular intervals. The length of this task can vary between 30 and 60 min. While this task is sensitive to vigilance fluctuations that arise as a result of sleep deprivation, it can be long and boring (Makeig, S & Inlow, M. 1993).

Auditory Discrimination Task

The task modified by Williams, H.L. (1962) and Jancke, L. (1998) gives out five tones (200, 300, 500, 700, 1000 Hz), which will be played at 95dB through a loud speaker. The subject is instructed to press a pre-specified button to indicate a “yes” response when he hears the 1000 cycle critical tone. He is instructed to press another button to indicate a “no” response when he hears any of the non-critical tones. Stimuli were 16-bit, digitally sampled tones (pure sine waves) of 500 ms duration each. The

inter-stimulus interval was 1 s. A set of 30 tones would be presented in each set. Among these tones, eight critical tones were randomly distributed.

Further modified test is the number sequence task from above. The stimulus consist of the sound of “one” “two” “three” “four” with random sequence. The subjects have to press the preset button of each sound of number immediately after the sound finished. The sequences of the numbers have to be remembered before the buttons are to be pressed. The accuracy will be strictly according to the pressing each buttons correctly.

The two modified auditory based tasks are the main brain activity detection tasks throughout this whole fatigue investigation. For the purpose to reduce the artifact from the eyes for both fMRI and EEG signal, the auditory task becomes the best methods to find out the mechanism of fatigue throughout the whole day without sleep. The investigation is based on the auditory task; also the general fatigue related brain activation and activity will be concluded.

2.4. Technology developed for fatigue investigation

2.4.1. The physiology of brain activation

Functional brain imaging can be strictly or more broadly defined. Different techniques are sensitive to different types of change. In contrast to many of the in vitro methods used to define brain function, methods used in vivo generally are concerned not with the behaviors of single neurons but with the activities of large populations of neurons. As we know, single neurons do not work independently, but function in large aggregates. Information transfer in the brain along axons occurs by electrical conduction. Information is transferred between neurons by the release of

neurotransmitter molecules at synapses and their subsequent interactions with specific receptors on target neurons. These neurotransmitter-receptor interactions then lead to changes in membrane current flow which change the post-synaptic neuronal membrane potential (and the accompanying extra cellular electrical field) and alter depolarization frequency. Most of the energy is used at or around synapses. As normal brain energy production depends ultimately on oxidative metabolism, there thus is greater local demand for delivery of oxygen with increased synaptic activity. To meet this increased metabolic demand, neuronal activation is accompanied by increased local blood flow.

In 1890, the physiologist Charles Sherrington demonstrated that stimulation of the brain caused a local increase in blood flow. However, he also observed that the relative proportion of oxygen extracted from this blood was reduced: the increase in total oxygen delivery exceeded the increase in oxygen utilization. The increased rate of oxygen delivery to the working brain shows that rates of oxygen diffusion from capillaries may limit its utilization rate (Kuwabara et al. 1992; Buxton and Frank 1997). By increasing the relative proportion of oxygenated hemoglobin in blood, the oxygen gradient between capillaries and cell mitochondria is increased, helping to match diffusion-limited transport to the rate of utilization. Accompanying the increase in blood flow is a small increase in local blood volume.

These elements of the physiology of information transfer in the brain-generation of an extra cellular electrical potential, increased oxidative metabolism (and glucose substrate utilization), and enhanced local blood flow and relative oxygenation – provide the basis for a number of functional imaging methods.

Functional imaging methods define dynamic brain changes having a time course similar to that of brain sensory, motor or cognitive activities. Specific interpretations demand methods that also can define the neuroanatomical localizations for these dynamic changes.

Different functional brain imaging methods, therefore, are usefully compared and contrasted in terms of both their temporal and spatial resolution. In general, electrophysiological methods based on direct mapping of transient brain electrical dipoles generated by neuronal depolarization (e.g. EEG) or the associated magnetic dipoles (e.g. MEG) define the underlying cortical neuronal events in real time (10-100msec), but provide relatively poor spatial resolution (many mm--cm). in contrast, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provide information on the increases in blood flow accompanying neuronal activation with relatively high spatial resolution (approximately, 1mm—10mm), but have a temporal resolution limited (at best) by the rate of the much slower haemodynamic changes that accompany neuronal depolarization.

Optical imaging methods (e.g. near infrared spectroscopy or NIRS) also measure changes in cortical blood flow, but, because of light scattering particularly the skull, have poor spatial resolution unless the cortical surface is exposed. Optical imaging methods also are restricted to study of the cortical surface. An important relative advantage of PET or fMRI methods is that they allow mapping of neuronal activation deep in the brain. Metabolic imaging by magnetic resonance spectroscopic imaging (MRSI) or PET is also possible, but these methods have a more variable and generally

lower spatial resolution (depending on the nature of the chemical species being imaged) and rather poor temporal resolution (on the order of 30s to min). However, the specificity of the information that they can provide is high and complements that available from fMRI.

2.4.2. Principles of magnetic resonance imaging (MRI)

Like its predecessor, x-ray computed tomography (CT), magnetic resonance (MR) is a computer-based imaging modality that displays the body in thin tomographic slices. Unlike CT, which requires ionizing radiation, MR is based on an apparently safe interaction between radio waves and hydrogen nuclei in the body in the presence of a strong magnetic field. Physical characteristics of a volume element, or voxel, of tissue are translated by the computer into a two-dimensional image comprised of picture elements, or pixels.

Very briefly, magnetic resonance arises from the interaction of nuclei which have a magnetic moment with an applied magnetic field (Hashemi and Bradley, 1997). Nuclei of many atoms with a nuclear "spin" can behave as simple magnetic dipoles and notionally can assume either a high-energy state (behaving as if oriented against the applied field) or a low-energy state (as if aligned with the applied magnetic field). Transitions between the two energy states accompany absorption or emission of energy in the radiofrequency range.

The frequency of the energy emitter by an excited nucleus is proportional to the magnetic field experienced. The magnetic field at the nucleus is determined primarily by the strong magnetic field that is applied to the sample in the imaging experiment.

As the precise relation between the resonance frequency and the applied magnetic field is different for different nuclei, magnetic resonance imaging systems can be "tuned" to detect specific types of nuclei independently. However, the magnetic field at the nucleus is also modulated by small "shielding" effects of electrons around the nucleus. These "shielding" effects cause changes on the order of only ppm in the precise resonance frequencies of nuclei that are observed. These small differences between resonance frequencies of protons in different molecules are ignored in conventional MRI or fMRI applications, but they provide the basis for MR spectroscopic methods.

The construction of an image by nuclear magnetic resonance (MR) techniques typically involves three different electromagnetic fields. 1) A high-intensity magnetic field aligns the magnetic dipoles of atomic nuclei, producing magnetization. 2) A brief "burst" of impulses in an RF field displaces the magnetization from its alignment with the main magnetic field and initiates a top like spinning that produces the MR signal. 3) A ramp like magnetic field placed across the exposed tissue and oscillating at a few cycles per second produces a magnetic gradient that slightly shifts the spin frequency, thereby providing position information as a function of spin frequency.

2.4.3. Blood oxygenation level dependent (BOLD) fMRI

The present study seeks to examine the physiological changes in brain activity as a result of sleep deprivation using BOLD fMRI. BOLD fMRI (blood oxygen level dependent functional magnetic resonance imaging) is one of the many functional imaging methods available for the mapping of brain activity in a time course

comparable to that of brain cognitive, sensory or motor activities (Matthews, 2001), and is responsible for making the identification of large-scale activation patterns associated with high-order cognitive processes possible (Cabeza & Nyberg, 2000). As opposed to in vitro methods which are concerned with the study of individual neurons, the in vivo method of fMRI concentrates on studying large populations of neurons, thus providing more useful information since neurons function in large aggregates and not individually. One distinct advantage fMRI has over other techniques is that it enables neuronal activations deep in the brain to be mapped, in terms of magnitude and neuroanatomical localizations. In addition, in comparison to the other imaging methods (for example, electroencephalography, commonly known as EEG), which map transient brain electrical dipoles generated by electrical depolarization, or near infrared spectroscopy (NIRS), which measures changes in blood flow), fMRI is able to provide information regarding neuronal activation with a relatively high spatial resolution at 1- 10 mm (Matthews, 2001) and this is one reason for its relative popularity.

Under normal conditions the brain derives almost all of its energy from the oxidation of glucose: for this it needs a nearly constant supply of glucose and oxygen, delivered by the blood supply through a rich network of vessels. Although the brain accounts for only about 2 per cent of the total body mass, it consumes 20 per cent of the body's glucose and oxygen, and receives 20 per cent of its blood supply. A remarkable feature of brain metabolism, fundamental to many functional imaging methods, is that blood flow and energy metabolism is tightly linked to local neuronal activity. This implies that maps of local glucose consumption, local oxygen consumption, or local blood flow each provide information on neuronal activity. The cellular and subcellular

sites of the increases of glucose and oxygen metabolism accompanying brain activation have been the subject of much investigation (Rose, 1975; Muir etc. 1991; Poitry-Yamate and Tsacopoulos, 1992; Magistretti etc. 1999). There is evidence that the major site for increased glycolysis with neuronal activity occurs in presynaptic structures (Eisenberg etc. 1993; Sokoloff etc. 1996; Sokoloff, 1999) which also may be the predominant location of lactate dehydrogenase (Borowsky and Collins 1989). Mitochondria, on the other hand, have been observed to be particularly concentrated in the postsynaptic structures of neuropil (Ribak, 1981; Gonzalez-Lima and Jones 1994), which stain weakly for the glycolytic enzyme hexokinase (Snyder and Wilson, 1983). These observations suggest that the glycolytic and oxidative metabolism preferentially occur in separate cellular compartments (Aoki etc. 1987). The observation of relative metabolic compartmentation would suggest that the enhanced metabolism associated with brain activation should occur primarily in postsynaptic structures which are subject to direct-current depolarization during neuronal excitation.

The locally increased blood flow in regions of the brain that become active appears to be a consequence of increased energy utilization at the synapse (Duncan etc. 1987; Duncan and Stumpf, 1991). Precisely which processes account for the metabolic changes is unclear. A major contribution to increased energy utilization may arise from metabolic changes in adjacent astrocytes with the uptake of the excitatory neurotransmitter, glutamate (Magistretti and Pellerin, 1996). The observations highlight fundamental characteristics of the BOLD fMRI response. First, it should be useful for identifying activation-related changes in grey matter. Second, the changes measured reflect synaptic activity or a combination of synaptic and dendritic electrical

changes, but not neuronal activity directly. Third, as cortical signal change are triggered by excitatory synaptic activity, at least under some conditions there should be a direct relationship between neuronal discharge rate and the magnitude of the BOLD response (Rees etc. 2000). However, the relationship should be modulated by the relative inhibitory input. Under some conditions at least, increases in inhibitory synaptic input may also contribute independently to increase in the fMRI BOLD signal.

Multiple mechanisms interact in the control of blood flow to the brain. Global brain perfusion is regulated by sympathetic, hormonal and myogenic mechanisms. Local tissue perfusion demands additional, more specific regulation to meet changes in energy demands with neuronal activation. There are a variety of factors likely to contribute to this local response, including +K release with neuronal depolarization and +H and adenosine release when there is a mismatch between oxygen delivery and utilization. However, nitric oxide (primarily from neuronal nitric oxide synthase) is likely to be the most important chemical signal responsible for local increases in perfusion with neuronal activation and also the cerebral vasodilatory response to hypercapnia.

Understanding the BOLD response is important for appreciating aspects of fMRI, including the spatial and temporal limitations to activation mapping, optimization of those responses and their potential change with pathology.

BOLD fMRI images signal contrast arising from changes in the deoxyhaemoglobin-oxyhaemoglobin ratio as an index for neuronal activation. Normal

blood can be considered as a concentrated solution of haemoglobin (Matthews, 2001). When bound to oxygen, haemoglobin is diamagnetic, while deoxygenated haemoglobin is paramagnetic. Normal brain energy production depends on oxidative metabolism. A large proportion of this energy is used at or around synapses to facilitate metabolic changes in the neurons and glia for the release of neurotransmitters in response to neuronal activation. With neuronal activation, there is therefore an increased blood flow in order to meet the increased metabolic demand. Increased synaptic activity therefore results in a greater local demand for oxygen delivery (Duncan & Stumpf, 1991). The imaging contrast employed in BOLD fMRI arises as a consequence of the higher ratio of oxy- to deoxyhaemoglobin in local draining venules and veins as a result of neuronal activation. As magnetic flux is reduced in diamagnetic materials (that is, the applied magnetic field is repelled) but increased in paramagnetic materials (that is, the applied magnetic field is attracted into the material), the change in haemoglobin oxygenation therefore leads to changes in local distortions of a magnetic field applied to it thus leading to a signal in the fMRI field..

2.4.4. Overview of fMRI analysis

After an fMRI experiment has been designed and carried out, the resulting data must be passed through various analysis steps before the experimenter can get answers to questions about experimentally-related activations at the individual or multi-subject level. After the experiment, more than 100 volumes of what are typically got. Each session a low resolution functional volume is acquired in very few seconds. Some of the imaging is taken while there is stimulation, and some are take while the subjects are at rest. As the image taken from the MR sequence we discussed before, which is

sensitive to the local blood oxygenation level (BOLD) change, parts of the images taken during stimulation should show increased intensity, compared with those taken whilst at rest. The parts of the images which show increased intensity should correspond to the brain areas which are activated by the stimulation. The aim of the fMRI analysis is to detect those parts of the brain which show increased intensity at the points in time that stimulation was applied.

Before the fMRI data analysis, there are several steps to do, which we call the preprocessing. Slice-timing correction, motion correction, intensity normalization will be taken. The purpose of the preprocessing is to remove various kinds of artifacts in the data, and to condition the data, in order to maximize the sensitivity of later statistical analysis, and also to increase the statistical validity.

A set of coplanar T2 anatomical images acquired in an identical orientation was used to align the functional images to the high resolution three-dimensional anatomical image. The high-resolution anatomical reference image was acquired using a T1 3D-MPRAGE sequence for the purpose of image display in Talairach space. The resulting aligned dataset was then transformed into Talairach space (Talairach and Tournox, 1988)

After that, statistical analysis is carried out to determine which voxels are activated by the stimulation. This can be simple correlation analysis or more advanced modeling of the expected haemodynamic response to the stimulation. It is most common to analyse each voxel's time series independently. Standard general linear model (GLM) sets up a model and fits it to the data. If the model is derived from the timing of the

stimulation that was applied to the subject in the MRI scanner, then a good fit between the model and the data means that the data was probably caused by the simulation. We consider the fitting of models to a single voxel's time-course.

A very simple example of linear modeling is

$$y(t)=\beta^* x(t) + c + e(t) \qquad (1)$$

where y(t) is the data, x(t) is the model, β is the parameter estimate for x(t), that is the value that the square wave (of height 1) must be multiplied by to fit the square wave component in the data. c is a constant, which would correspond to the base line (rest) intensity value in the data. e is the error in the model fitting. Thus the model fitting involves adjusting the baseline level and the height of the square wave, to best fit the data; the error term accounts for the residual error between the fitted model and the data.

2.5. Model of the fatigue

2.5.1. The existing model of the fatigue

From the physical to the psychological aspects understanding of the mental fatigue, now a general model of the fatigue states that fatigue is in the mind, not the muscles. Traditionally, fatigue was viewed as the result of over-worked muscles ceasing to function properly. But evidence is mounting that our brains make us feel weary after exercise mental or physical (New Scientist print edition, 20 March, 2004). The idea is that the brain steps into prevent vital organs damage by inducing fatigue.

There are number of models to explain the fatigue. The importance of the conceptual models described above is that they suggest that different physiological systems

determine performance under different conditions. In the study of the mental fatigue (Jongman, L. etc.), the model of working memory hypothesis of mental fatigue was proposed. Mental fatigue is defined as "a subjective feeling of fatigue combined with a negative change in performance, due to time spent on cognitively demanding tasks." Based on many authors of fatigue study (Bartlett, 1943; Broadbent, 1979; Holding, 1983), the behavior of the people seems to loose cohesion when they got mental fatigue.

2.5.2. The aims of the study

The study of mental fatigue has increased leaps and bounds, yet there is still no universal definition of mental fatigue. Researchers in this field have not been able to agree upon a single definition of fatigue, however, there is consensus amongst the scientific community that fatigue comprises of physiological, emotional and behavioral factors that can result in chronic physical or mental states. Picture 2-1 shows the schematic structure of the study.

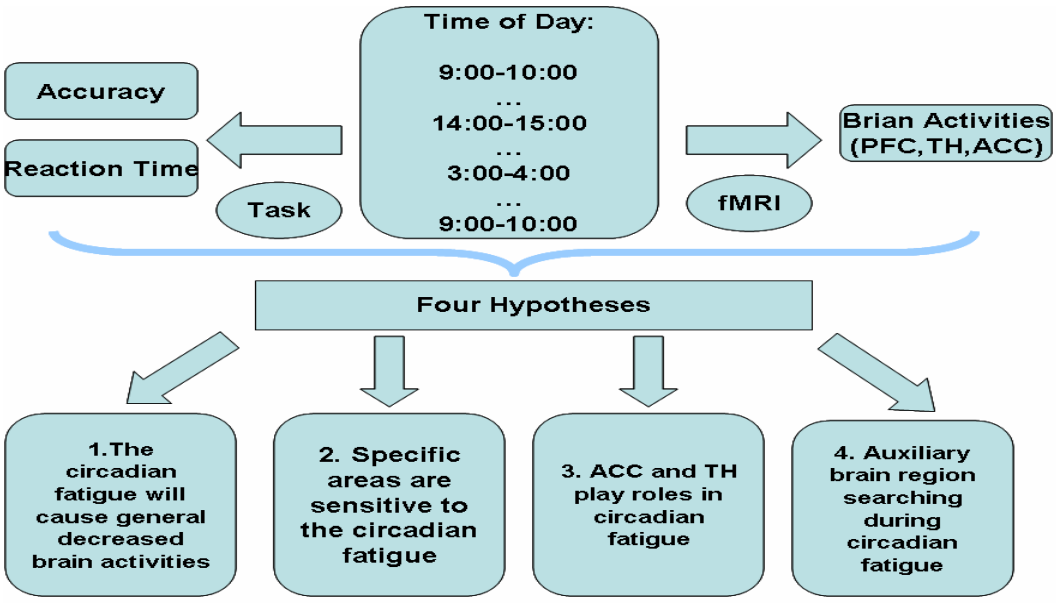


Figure 2-1: Schematic structure of the study

On the basis of earlier findings, the following aims to each of the four hypotheses will be achieved. Picture 2-1 shows the schematic structure of the study.

1. By comparing the general activity of the brain with the performance, we aim to find out the direct relation with the decrease activities of the two, which can explain the decreased performance with the brain fatigue.

2. By indicating the working memory in the auditory discrimination tasks, we hoped to find the activities of the PFC decreased dramatically as the fatigue progressed, as well as the activities of PL.

3. The ACC and TH, which are engaged in arousal and attention respectively, are also indicated in the auditory discriminate tasks. The increased activities of them are investigated, compared to the decreased performance.

4. Triggered by the steadily decreased performance which means the stable state in each fatigue levels, we are going to search the auxiliary brain regions as a feedback to the task specified central area.

3 Materials and Methods

3.1. Study Subjects

Fourteen right-handed neurologically healthy subjects (4 females and 10 males; age range 19-25 years old) recruited from the National University of Singapore or Nanyang Technology University of Singapore with the undergraduate education background gave the consent form to participate in the experiment. This study has been approved by Institutional Review Board. It is supported by the funding of …. Financial compensations for expenses are given for subjects' participation. All subjects were screened using a medical history, a sleep questionnaire, and one week of sleep diary records to establish that they had relatively regular sleep patterns. Only subjects who did not have a habit of napping were short listed. In addition, in order to find out the influence of the circadian rhythms to the mental fatigue, subjects were screened by fMRI based on the general time of inflexion of performance records which came to be 9am, 2pm, 3 am and 9am (2nd day).

3.2. Experimental protocol

In order to study the circadian fatigue, the time of the scanning was crucial. The subjects were asked to stay awake in National University Hospital out-patient clinic totally 25 hours. They were required to report to the laboratory at 8:30 am and were monitored onwards for 25 hours without sleep. For the whole experiment, subjects were scanned 4 times by fMRI, each for a different fatigue state. In addition to the fMRI scanning which took 1 hour for each time, EEG was recorded each hour during

the period of 25 hours sleep deprivation. They were not allowed stimulants of any kind during the whole experiment. Subjects' performance on Auditory Discrimination Task (ADT) which is the objective method measuring fatigue, as well as the Epworth Sleepiness Score (ESS) and Stanford Sleepiness Scale (SSS) which are the subjective methods measuring fatigue was recorded hourly. The subjective evaluation of fatigue states – ESS and SSS were scored by subjects before and after ADT. The performance accuracy and Reaction Time (RT) on the ADT was also recorded. In both the fMRI and EEG recording, subjects performed the ADT for the target tone discrimination (TTD) and number sequence discrimination (NSD) task. The session consisted of four runs (2 TTD runs and 2 NSD runs). Each fMRI experimental session lasted 55 minutes and each EEG experimental session lasted 15 minutes. The experimental protocol was approved by the Ethics Committee of the National University of Singapore.

3.3. Auditory Discrimination Task

The ADT task was administered to the subjects while they were in the fMRI scanner. It requires the continuous discrimination ability based on the different fatigue state. All subjects were given a presetting session, and were included only after reaching a criterion level of performance (>75% accuracy). During each hour, subjects had to do the task twice – one for fMRI and one for EEG recording.

3.3.1. Target tone discrimination (TTD) Task

The stimuli consisted of five tones with different frequencies which are 200Hz, 300Hz, 500Hz, 700Hz, and 1000Hz. The tones were delivered at 95dB through headphones. The 1000Hz tone is the critical tone which is the target tone to be

discriminated from the other tones. In each run, six experimental blocks alternated with seven baseline resting blocks, starting and ending with a resting block. In each block, 15 tones were presented through the headphone, with each for 500 ms and a 1,500 ms inter-stimulus interval for subjects making response. There are only 4 critical tones within 15 tones. All the tones are randomly distributed. The tone stimuli were 16-bit, digitally sampled tones (pure sine waves) of 500ms duration each. The total time of the TTD test took 6 minutes and 42 seconds (Figure 3-1).

The task requires the subjects to make a response indicating whether the stimulus is the target or the non-target using hand-held response box. Upon hearing the 1000Hz cycle critical tone, the subjects had to press the right button to indicate a "yes" response as soon as they can. On the other hand, whenever they hear any of the non-critical tones, they are to press the left button to indicate a "no" response as soon as possible. Meanwhile the RT and the accuracy were recorded.

3.3.2. Number Sequence Discrimination (NSD) Task

The stimuli consisted of groups of 4 numbers which are one, two, three and four. The sound of the numbers was delivered at 95dB through headphones. The sequence of the 4 numbers has to be remembered and the subjects had to make the same sequence response indicated on the key box. In each run, six experimental blocks alternated with seven baseline resting blocks, starting and ending with a resting block. In each block, 6 groups of the number 1,2,3,4 were presented, with each group for 3,000 ms and a 2,000 ms inter-stimulus interval for subjects making response (Figure 3-1). The numbers were randomly sequenced. The sound stimuli were 16-bit, digitally sampled tones of 500 ms duration each. The total time of the NSD test also took 6 minutes and

42 seconds. After hearing the sequenced numbers, the subjects had to press the numbers on the button in the same sequence quickly. Accuracy was recorded.

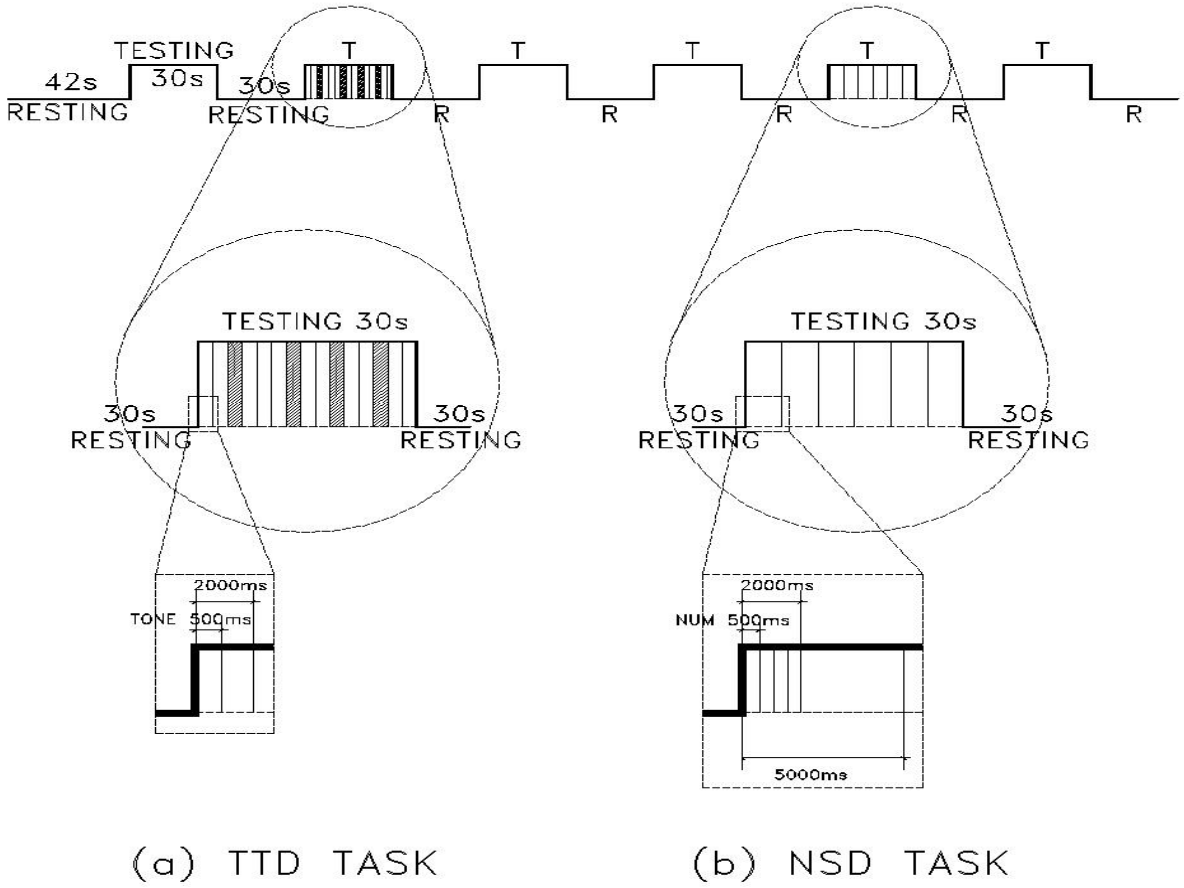


Figure 3-1: Schematic representation of the TTD and NSD task

3.4. fMRI scanning procedures

Stimuli were instructed by the computer and heard by subjects through an earphone. A tightly clip was used to reduce any possible head-motion of the subject. All images were acquired with a 1.5T scanner (Siemens, Symphony Germany). A blipped gradient-echo EPI sequence was used with TR = 3000ms, FOV = 256 x 256 mm and 64 x 64 mm pixel matrix. 32 oblique axial slices with thickness 3 mm (0.3mm gap) approximately parallel to the anterior and posterior commissure (AC – PC) line were acquired.

3.5. Behavioral data analysis procedures

The accuracy and reaction times were recorded for each subject. For the present study, the design of the task is that a response was required for each stimulus in all states. Any response which was not coincident with the requirement was regarded as an incorrect response while accuracy was calculated based on the proportion of trials answered correctly. As such, the null response, the wrong button pressing, the wrong sequence response, less or more response is all labeled as incorrect. Analysis of behavioral measures was performed using repeated measures ANOVA with state (4 stages from alert to fatigue after 25 hours awake) as within-subject predictors using MiniTab (version 14.12).

3.6. Image analysis procedures

Functional images underwent phase correction prior to further processing with Brain Voyager QX software version 1.3 (Brain Innovation, Maastricht, Netherlands). Mean intensity adjustment and intra-session alignment were performed on functional images.

Gaussian filtering was applied in the spatial domain with a smoothing kernel of 8 mm FWHM for computation of group-level activation maps and 4 mm FWHM for individual-level activation maps. A set of coplanar T2 anatomical images acquired in anidentical orientation was used to align the functional images to the high resolution three-dimensional anatomical image. The high-resolution anatomical reference image was acquired using a T1 3D-MPRAGE sequence for the purpose of image display in Talairach space. The resulting aligned dataset was then transformed into Talairach space (Talairach and Tournox, 1988). Stereotaxic coordinates in the x dimension refer in millimeters to the medial-to-lateral distance from the midline, in the y dimension to the anterior-posterior distance, and in the z dimension to the superior-inferior distance from the intercommisural line (see Figure 3-2).

Image data analysis was performed at the group or multisubject level. The imaging data was analyzed by a general linear model (GLM) with state (rest state versus levels of circadian fatigue) as within-subject predictors.

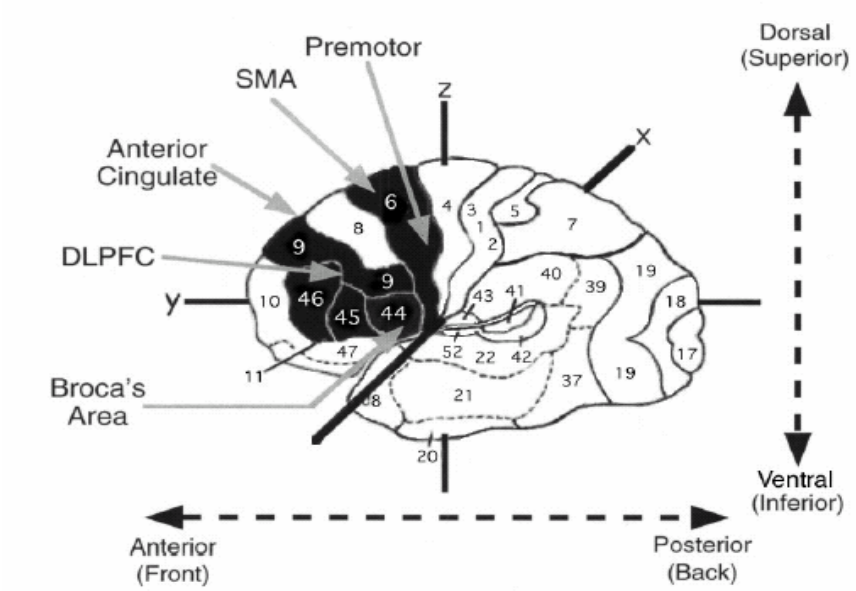


Figure 3-2: Schematic representation of the left lateral cortex. Major prefrontal areas have been annotated (numbers correspond to Brodmann areas). Boxed areas indicate some of the regions of interest which will be focused on in the present study. Also indicated are the x, y, and z dimensions, which are used to report the coordinates of activation (where the three dimensions intersect, the coordinates are zero). The anterior-posterior and dorsal-ventral directions which are used in anatomical descriptions are also indicated. Adapted from Smith and Jonides (1999).

The expected BOLD signal change was modeled using a gamma function (tau = 1.25, delta = 2.5) synchronized to blocks of cognitive tasks. Time courses were collected from activated voxels 20 x 20 x 20 mm^3 which passed a threshold of $p<0.005$, and were averaged across blocks of the same condition for each participant. The averaged values were then fitted to the GLM and the parameter estimates (beta) for each ROI for each predictor harvested from the best fit of the GLM on these voxels. A conjunction analysis was first applied to the GLM to derive areas common to all tasks and conditions. These values were then subjected to repeated-measures ANOVA with state (rest state versus levels of circadian fatigue state) as within-subject predictors. Contrast operations (session 2, 3, 4 minus session 1) were subsequently applied to the group-level GLM activation maps. Each participant's mean parameter estimate across voxels for each contrast for each predictor was calculated and subjected to ANOVA to find out the difference significance.

3.7. fMRI signal evaluation

Individual analyses were performed for the ROIs: DLPFC, VLPFC, AFC, parietal cortex, primary motor cortex, temporal cortex, ACC and TH. ROIs were defined by a combination of functional activation and anatomical landmarks. This approach considered activated voxels within the anatomically defined ROI without including areas that lay in the ROI but were not activated above threshold. The PFC comprised 3 areas, namely the DLPFC, VLPFC, and the AFC. The DLPFC ROI included the middle frontal gyrus which corresponds to BA 46 and the dorsal part of the inferior frontal gyrus corresponding to BA 9 while the VLPFC ROI included the ventral part of the inferior frontal gyrus corresponding to BA 44, 45 and 47. The anterior frontal cortex (AFC) incorporated the "frontopolar area lying anterior to the anteriormost extent of the inferior frontal gyrus" (Fletcher and Henson, 2001) and included BA 8 and 10. The parietal ROI incorporated the superior and inferior parietal lobes that included BA 7 and 40. The ACC ROI included areas which corresponded to BA 24 and 32. The primary motor cortex ROI included the BA 4. The temporal ROI incorporated the superior, inferior and medial temporal lobes where the primary auditory cortex is located (BA 41, 42).

4 Results

4.1. Behavioral data for the different states as a function of time of the day

The subjects (SDS2, SDS7 and SDS10) were excluded from the behavioral data analysis as they were outliers. Three subjects (SDS1, SDS5 and SDS6)'s data was discarded because they were unable to complete the study. The means and standard deviations of the two behavioral measures, task accuracy and reaction times (RT), were summarized in Figure 4-1. Time of the day appeared to interfere with cognitive performance. All the subjects showed an overall decrease in the percentage of correct responses and took longer to respond (Table 4-1).

Table 4-1: The accuracy and the RT of the NSD and TTD task. The accuracy refers to the percentage and the RT refers to the unit of ms.

a) NSD task accuracy

Subjects / Time	S3	S4	S8	S9	S11	S12	S13	S14	Mean	SD*
9:00	95.8	95.8	91.7	90.3	98.6	95.8	97.2	91.7	94.6125	2.985411
14:00	98.6	97.2	97.2	100	97.2	97.2	90.3	100	97.2125	3.053072
3:00	84.7	81.9	94.4	95.8	88.9	95.8	61.1	100	87.825	12.41494
9:00	90.3	63.9	97.2	97.2	90.3	98.6	75	98.6	88.8875	12.80674

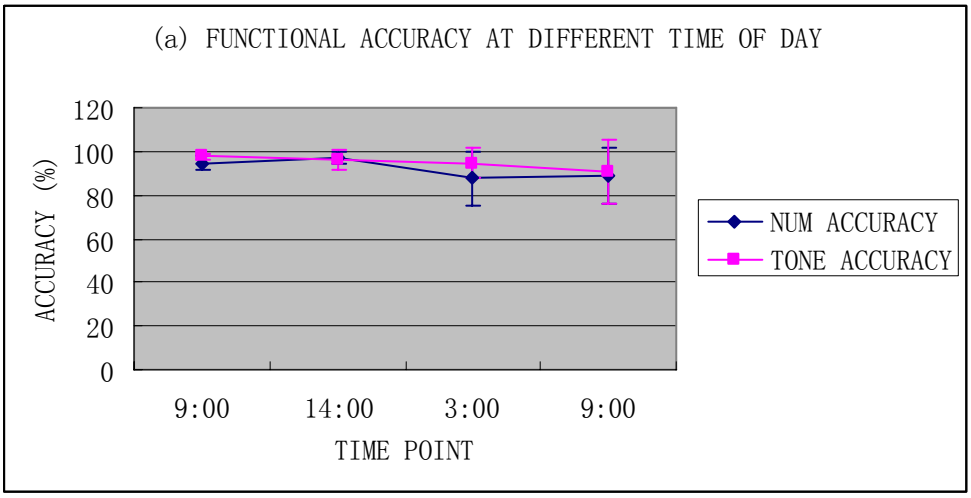
b) TTD task accuracy

Subjects / Time	S3	S4	S8	S9	S11	S12	S13	S14	Mean	SD*
9:00	100	96.7	98.9	94.4	98.3	97.2	96.7	98.4	97.575	1.715268
14:00	97.8	98.9	100	94.4	98.9	96.7	85.6	98.9	96.4	4.696503
3:00	96.7	92.8	100	94.4	93.9	100	79.5	100	94.6625	6.799567
9:00	95.6	96.7	98.3	94.4	87.8	97.8	54.5	100	90.6375	15.05788

c) TTD task RT

Subjects / Time	S3	S4	S8	S9	S11	S12	S13	S14	Mean	SD*
9:00	740.83	773.33	420.55	462.50	606.11	531.38	706.38	527.77	596.11	132.09
14:00	791.11	646.94	393.88	385.55	716.66	457.22	886.66	533.88	601.49	188.11
3:00	763.05	966.11	435.83	389.72	861.94	454.16	1009.72	501.38	672.74	255.49
9:00	794.44	636.66	457.22	390.55	714.44	454.16	1365	557.49	671.25	312.63

SD*: standard deviation



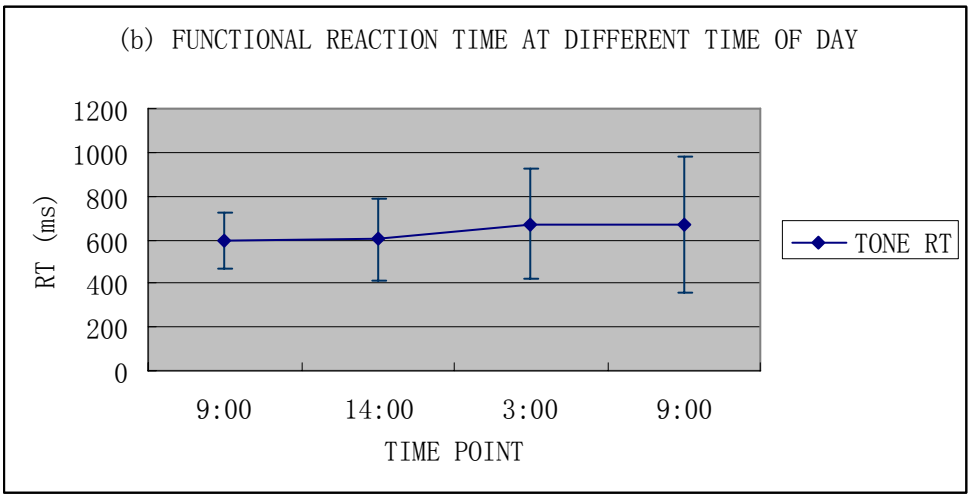


Figure 4-1: Means and standard errors of the behavioral data during the fMRI session as a function of time of day (from 9am 1st day to 9am 2nd day): (a) Accuracy of TTD and NSD task (b) Reaction times of TTD task

In addition, there appeared to be a trend with regard to both task. An increase in time progress was generally accompanied by a decrease in accuracy and an increase in RT. However, repeated ANOVA analysis for both behavioral measures failed to establish any significant effect state (Table 4-2).

Table 4-2: Repeated ANOVA analysis for both behavioral measures

a) NSD task accuracy

Source	DF	SS	MS	F	P
1	3	488.3	162.8	1.94	0.147
Error	28	2354.6	84.1		
Total	31	2843.0			

S = 9.170 R-Sq = 17.18% R-Sq(adj) = 8.30%

Level	N	Mean	StDev	Individual 95% CIs For Mean Based on Pooled StDev
1	8	94.61	2.99	(----------*----------)
2	8	97.21	3.05	(----------*----------)
3	8	87.83	12.41	(----------*----------)
4	8	88.89	12.81	(----------*----------)

84.0 90.0 96.0 102.0

Pooled StDev = 9.17

b) TTD task accuracy

Source	DF	SS	MS	F	P
1	3	220.8	73.6	0.99	0.413
Error	28	2085.8	74.5		
Total	31	2306.6			

S = 8.631 R-Sq = 9.57% R-Sq(adj) = 0.00%

Level	N	Mean	StDev	Individual 95% CIs For Mean Based on Pooled StDev
1	8	97.58	1.72	(-----------*-----------)
2	8	96.40	4.70	(-----------*-----------)
3	8	94.66	6.80	(-----------*-----------)
4	8	90.64	15.06	(-----------*-----------)

85.0 90.0 95.0 100.0

Pooled StDev = 8.63

c) TTD task RT

Source	DF	SS	MS	F	P
1	3	42984	14328	0.27	0.850
Error	28	1510994	53964		
Total	31	1553978			

S = 232.3 R-Sq = 2.77% R-Sq(adj) = 0.00%

Level	N	Mean	StDev	Individual 95% CIs For Mean Based on Pooled StDev
1	8	596.1	132.1	(----------*----------)
2	8	601.5	188.1	(----------*----------)
3	8	672.7	255.5	(----------*----------)
4	8	671.3	312.6	(----------*----------)

480 600 720 840

Pooled StDev = 232.3

4.2. Imaging data analysis of the 4 sessions:

The imaging data of the three subjects who were outliers for the behavioral data were also excluded from the imaging analysis.

A conjunction analysis was performed to determine the areas consistently activated across the 4 sessions. Activation was observed in the following ROIs: bilateral ventrolateral PFC (VLPFC) (Brodmann areas (BA) 44, 45，BA 47); anterior frontal cortex (AFC) (BA 10), supplemental motor area (SMA) (BA 6); precentral gyrus (BA 4), thalamus, bilateral inferior and superior parietal lobes (PL) (BA 7), postcentral gyrus (BA 2) bilateral inferior and superior temporal lobes(TL) (BA 41, BA 37, 38), bilateral primary auditory cortex (BA 41); the precuneus (PCu) (BA 7) and insular (bilaterally); left cingulated gyrus (ACC) (BA 24, 30). The anatomical localizations along the axial plane of the various ROIs are shown in Figure 4-2. The significant effect of fatigue will be focused on these area: bilateral VLPFC, AFC, left precental gyrus, superior and inferior PL (bilateral), superior and inferior TL (bilateral), postcental gyrus, left ACC and the thalamus (Table 4-3).

Besides the regions as mentioned above, the main effect of the fatigue causing decreased activities of the brain was also found in these areas: bilateral AFC (BA 8, 10), left ACC (BA 31) (Table 4-4), and also bilateral hippocampus (BA 35) (Figure 4-3).

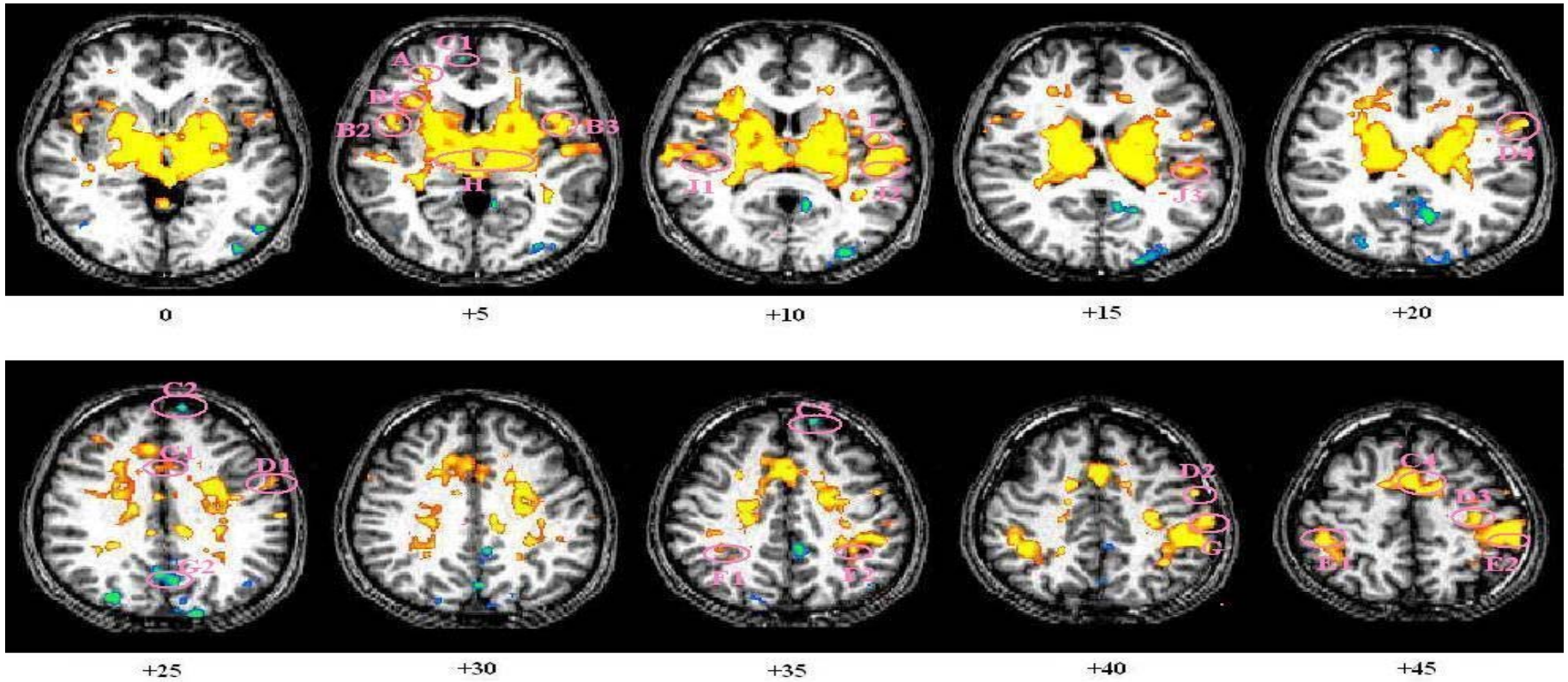


Figure 4-2: Regions of interest (ROI) maps showing axial sections after a conjunction analysis of summation of 4 sessions. The axial Talariach coordinates are indicated below for each slice of the brain at an interval of 5 mm from 0 to 45 mm. All activations have crossed the threshold p < 0.5e-3. The Talariach coordinates for regions of interest (indicated by circle) as follows: middle frontal gyrus: A(25, 41, 5); inferior frontal gyrus: B1(33, 21, 5), B2(43, 9, 5), B3(-43, 9, 5); superior frontal gyrus--GFs: C1(6, 50, 5); medial frontal lobe: C2(-9, 56, 25), C3(-12, 46, 37), C4(1, 6, 45); motor cortex: D1(-54, 3, 25), D2(-48, -4, 40), D3(-35, -18, 50), D4(-57, 5, 19); inferior parietal--LPi: F1(-33, -42, 38), F2(36, -42, 40); superior parietal--LPs: E1(42, -35, 40), E2(-43, -34, 40); sensory cortex: G(-53, -34, 44) ; thalamus: H(16, -17, 5), (-16, -17, 5); insula: I(-42, -7, 10); gyrus cinguli: G1(-4, 12, 37), G2(-5, -43, 33) precuneus-PCu(-5, -65, 25); Primary auditory receiving cortex—GTT: J1(41,-21,10) J2(-48, -24, 10), J3(-44, -29, 15).

Table 4-3: Talairach coordinates of significant effect of fatigue with constant active activity found as a summarization of all the 4 sessions. p < 0.5e-3.

Brain area	Anatomy	BA area	Talairach coordinates			Denote
			X*	Y*	Z*	
Right AFC	Middle frontal gyrus	10	25	41	5	A
Right VLPFC	Inferior frontal gyrus	45	33	21	5	B1
Bilateral VLPFC	Inferior frontal gyrus	47	+/-43	9	5	B2B3
Right SMA	Medial frontal gyrus	6	1	6	45	C4
------	Precentral gyrus	4	-54	3	25	D1
------	Precentral gyrus	4	-48	-4	40	D2
------	Precentral gyrus	4	-35	-18	50	D3
------	Precentral gyrus	4	-57	5	20	D4
Bilateral Temporal cortex	Primary auditory cortex	41	41	-21	10	J1
Left Temporal cortex	Primary auditory cortex	41	-48	-24	10	J2
Left Temporal cortex	Primary auditory cortex	41	-44	-29	15	J3
Left Parietal cortex	Inferior parietal lobe	40	-33	-42	38	F1
Right Parietal cortex	Inferior parietal lobe	40	36	-42	40	F2
Left Parietal cortex	Inferior parietal lobe	40	-53	-34	44	
Right Parietal cortex	Superior parietal lobe	40	42	-35	40	E1
Left Parietal cortex	Superior parietal lobe	40	-43	-34	40	E2
------	Postcentral gyrus	2	-53	-34	44	G
Left Parietal cortex	Precuneus	18	-5	-65	25	
Bilateral Thalamus	Thalamus	NA	+/-16	-17	5	H
Left Cingulate cortex	Cinguli Gyrus	24	-4	12	37	G1
Left Cingulatel cortex	Cinguli Gyrus	30	-9	-50	8	
Insular cortex	Insular		-42	-7	10	I

*X, Y, Z (in mm) refer to coordinates in the Talairach space in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure (AC).

Table 4-4: Talairach coordinates of significant effect of fatigue with constant reduced activity found as a summarization of all the 4 sessions. p < 0.5e-3.

Brain area	Anatomy	BA area	Talairach coordinates			Denote
			X*	Y*	Z*	
Left AFC	Superior frontal gyrus	8	-12	46	37	C3
Right AFC	Medial frontal gyrus	10	6	50	5	C1
Left AFC	Medial frontal gyrus	10	-9	56	25	C2
Left Cingulate cortex	Cinguli Gyrus	31	-5	-43	33	G2

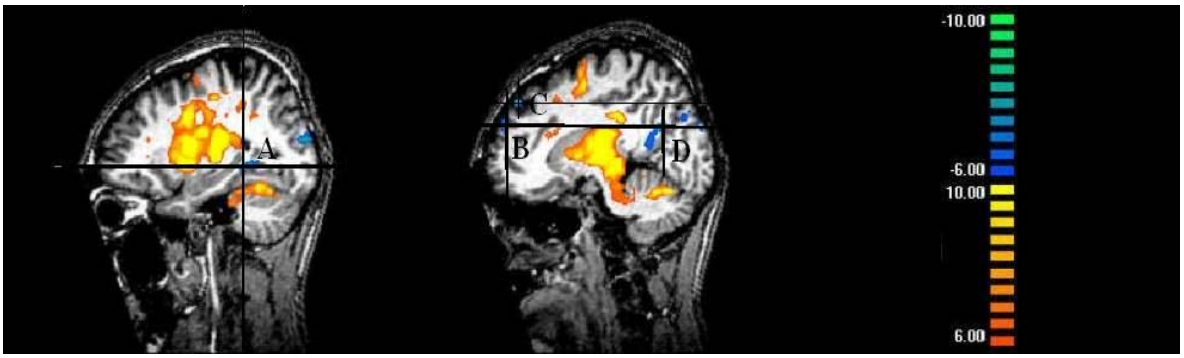


Figure 4-3: Reduced activity map showing sagittal sections of 4 session summation. A) Left hippocampus (-25,-44,-4); B) Left AFC (-12, 56, 21); C) Left AFC (-12, 46, 37); D) Left ACC (-12, -60, 21). P<0.5e-3.

4.3. Relation between fMRI activity and fatigue states

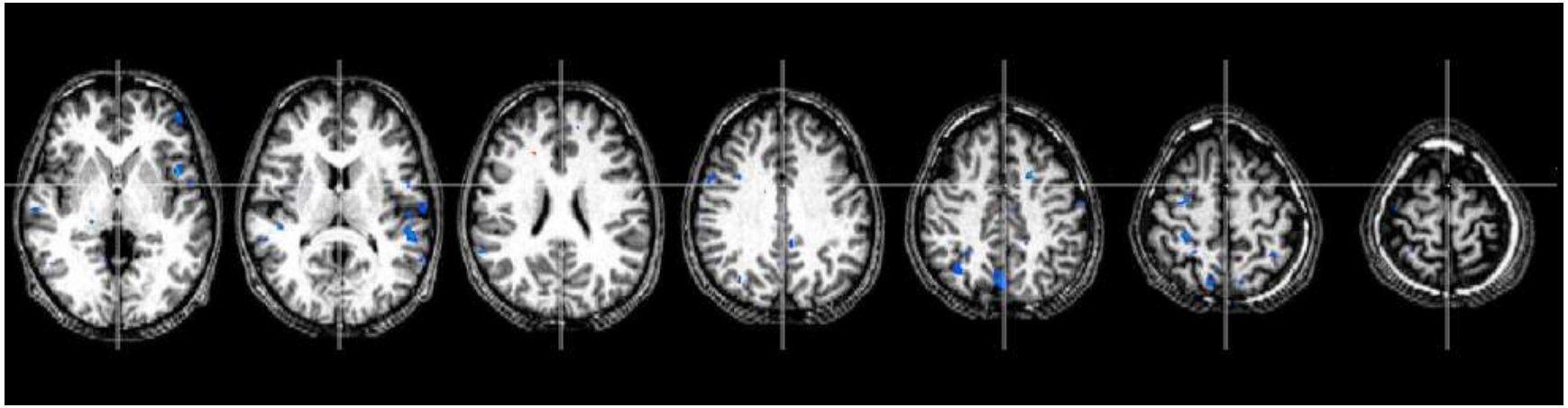
Analysis was performed individually at each session to determine how the activation signal varies with state. First using contrasts session 2 minus 1, session 3 minus 2, and session 4 minus 3 respectively, decreased brain activity (indicated as blue in the Figure 4-4) except some special parts which are the mid brain and the thalamus throughout the whole 4 sessions are shown in Figure 4-4.

Secondly, Using the contrasts session 2, 3, 4 minus session 1, areas more activated in the different fatigue state were identified at the different contrast (Figure 4-5 session 2 minus session 1, Figure 4-6 session 3 minus session 1 and Figure 4-7 session 4 minus session 1) and these have been summarized in Table 4-5 for session 2 minus session 1, Table 4-6 for session 3 minus session 1, and Table 4-7 for session 4 minus session 1..

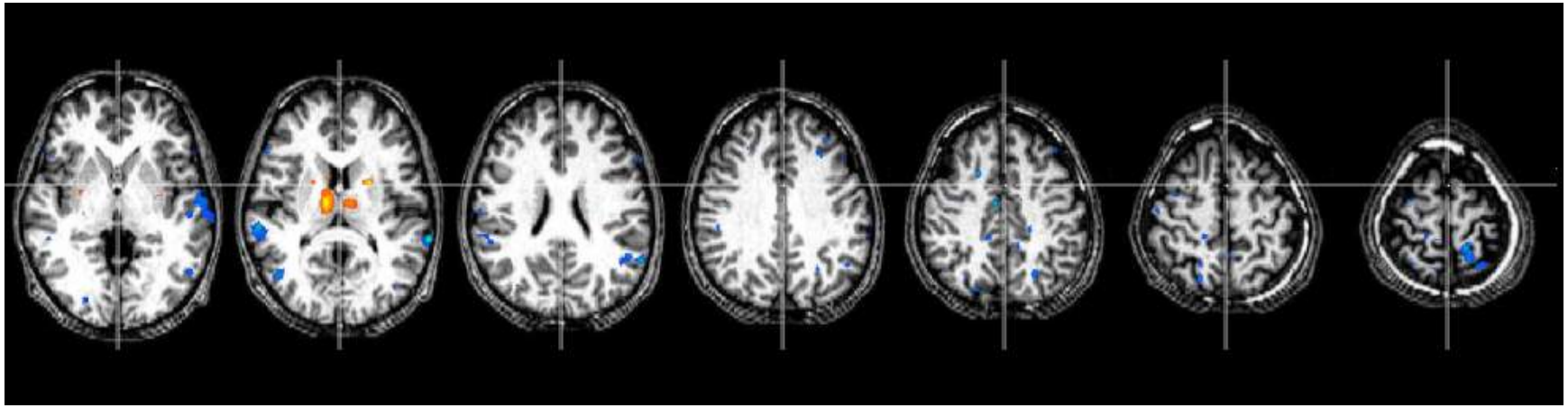
In the session 2 minus session 1, these areas were found to be more effected by the circadian fatigue with decreased activity: bilateral VLPFC, left SMA (BA 6), left AFC (BA 10), right parietal lobe (BA 7) and bilateral temporal lobe (Figure 4-5). The insular left side, an area not included as an ROI, was also found to be sensible to the circadian fatigue. In the session 3 minus session 1, increased activity of the brain due to the circadian fatigue was found in left AFC (BA 10), left SMA (BA 6), bilateral parietal lobe (BA 7) and temporal lobe, left cingulate cortex (ACC) (BA 31, 24) (Figure 4-6). Increased activity was observed in the left TH, an area which was not designated as the most important ROI. The right insular was also found to be decreased activity. In the session 4 minus session 1, circadian fatigue resulted in decreased activity in the left AFC (BA 10), right VLPFC (BA 47), bilateral DLPFC

(BA 9), left ACC (BA 31, 24), bilateral parietal and temporal lobe (Figure 4-7). Thalamus was also found to have increased activity and also the right ACC (BA 23).

A) 2-1



B) 3-2



C) 4-3

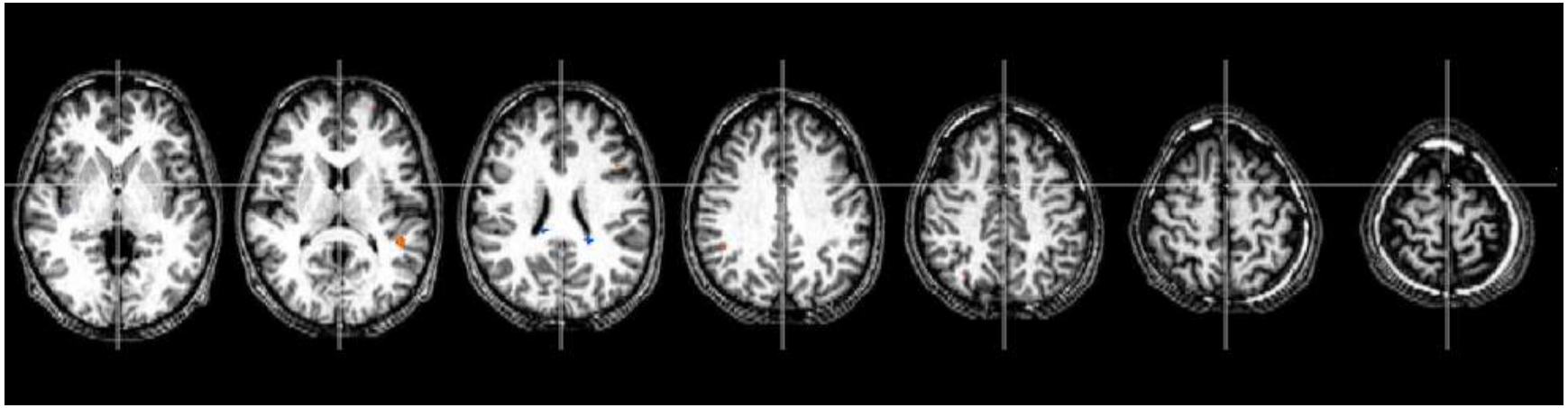


Figure 4-4: Activity indication throughout the whole 4 sessions with general decreased activity as the fatigue states progressing. The slices are got at the interval of 10mm from the 0mm in the horizontal direction. All the threshold are P<0.5e-3. A) The activity of the brain at the 2nd session minus the activity of the brain at the 1st session. The blue indicates the area with decreased activity during the 2nd session. B) The activity of the brain at the 3rd session minus the activity of the brain at the 2nd session. The blue indicates the area with decreased activity during the 3rd session. The red indicates the area with increased activity during the 3rd session. The thalamus and the midbrain are more active in the 3rd session. C) The activity of the brain at the 4th session minus the activity of the brain at the 3rd session. The blue indicates the area with decreased activity during the 4th session. The red indicates the area with increased activity during the 4th session.

Table 4-5: Talairach coordinates of significant activity (increased or decreased activity) within the same task (NSD) across states. Values are obtained using the contrasts at session 2 minus session 1

Brain area	Anatomy	BA area	Talairach coordinates			Denote
			X	Y	Z	
Left AFC	Middle frontal gyrus	10	-42	50	2	
Left VLPFC	Middle frontal gyrus	47	-38	37	-8	A
Right VLPFC	Inferior frontal gyrus	44	50	5	29	L
Session 2 minus session 1 continued						
Left SMA	Medial frontal gyrus	6	-1	6	57	P
--------	Precentral gyrus	4	-51	-17	34	M
Right Temporal cortex	Inferior temporal gyrus	37	48	-58	-5	D
Left Temporal cortex	Inferior temporal gyrus	37	-48	-61	-5	E
Left Temporal cortex	Superior temporal gyrus	38	45	6	-8	C
Right Temporal cortex	Superior temporal gyrus	38	-48	12	-8	B
Left Temporal cortex	Superior temporal gyrus	42	-57	-13	7	I
Right Temporal cortex	Superior temporal gyrus	22	59	-35	7	G
Left Temporal cortex	Superior temporal gyrus	22	-49	-34	7	H
Right Temporal cortex	Medial temporal gyrus	22	58	-33	4	
Left Temporal cortex	Primary auditory cortex	42	-50	-33	10	J
Right Parietal cortex	Inferior parietal lobe	7	33	-57	43	O
Right Parietal cortex	Superior parietal lobe	7	33	-40	55	Q
Right Parietal cortex	Precuneus	7	3	-67	40	N
Left ACC	Cinguli gyrus	23	-6	-40	26	K
Left Insular cortex	Insular	NA	-41	9	-2	F

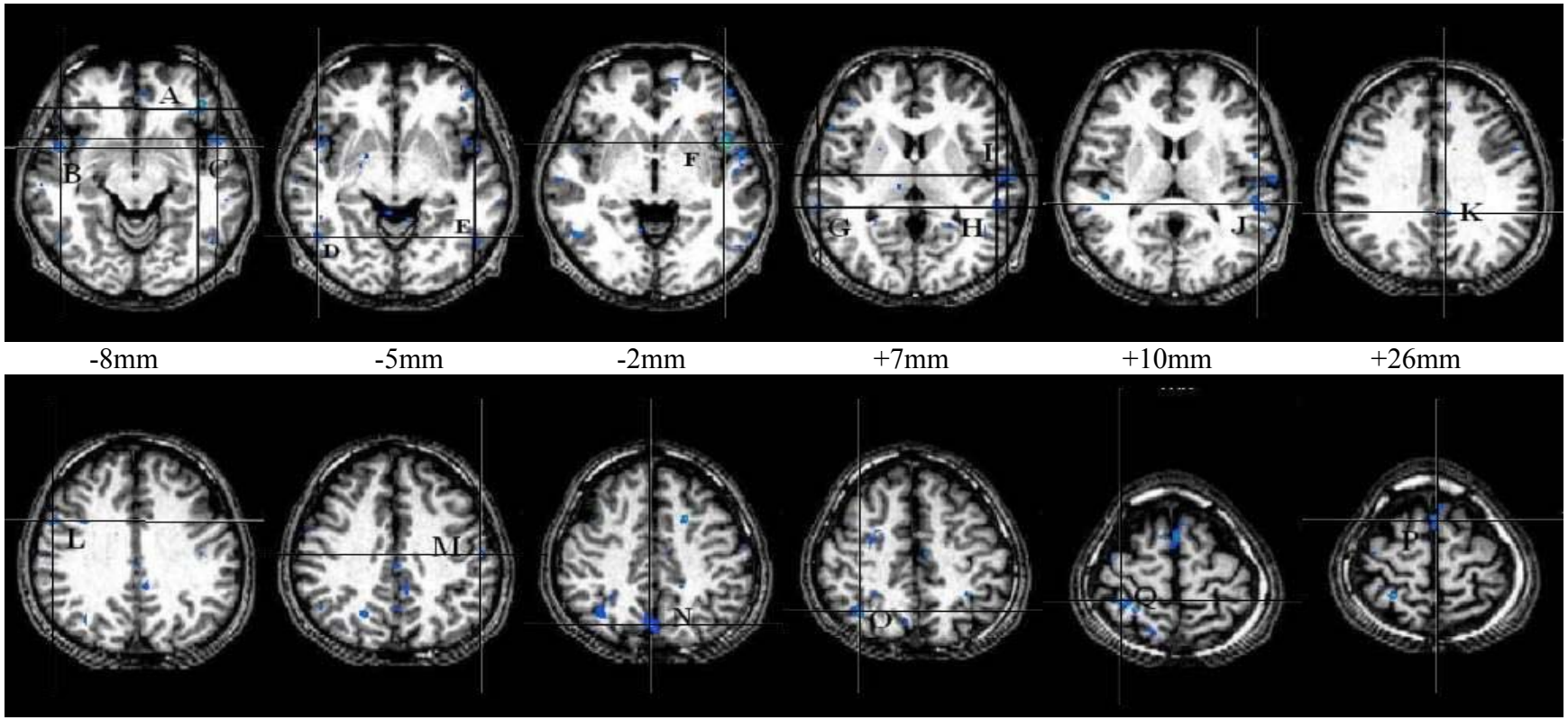
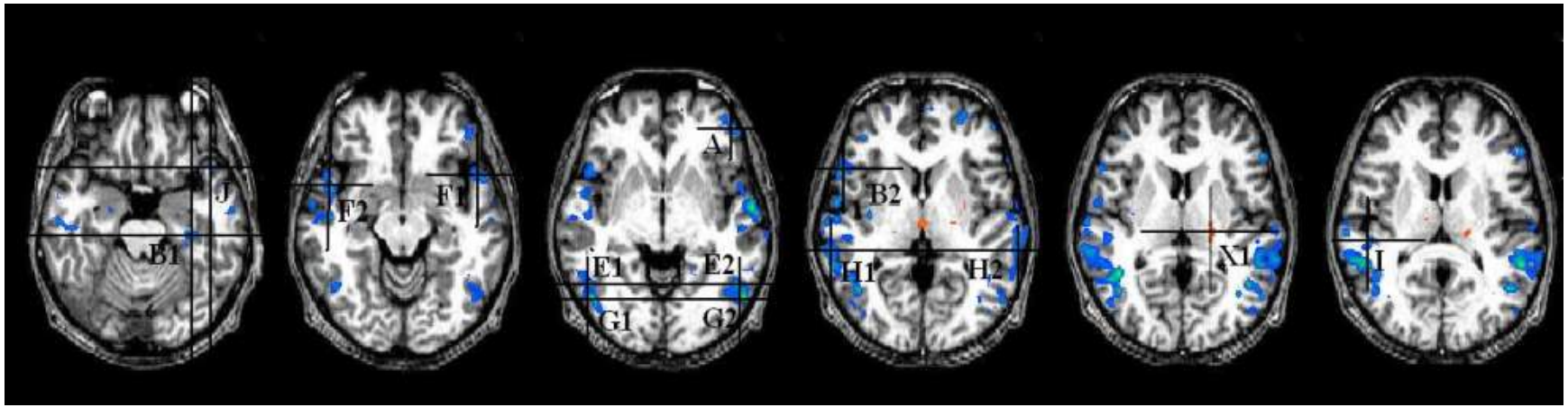


Figure 4-5: Group level activity maps observed with the contrasts session 2 minus session 1, P<0.5e-3. The Talaraich coordinates for the activity peak (indicated by cross) are as follows: upper row: A) Left VLPFC: -38, 37, -8; B) Left superiortemporal lobe: -48, 12, -8; C) Right superior temporal lobe: 45, 6, -8; D) Right inferior temporal lobe: 48, -58, -5; E) Left inferior temporal lobe: -48, -61, -5; F) Left insular cortex: -41, 9, -2; G) Right superior temporal lobe: 59, -35, 7; H) Left superior temporal lobe: -49, -34, 7; I) Left superior temporal lobe: -57, -13, 7, J) Left primary auditory cortex: -50, -33, 10; K)left cinguli gyrus: -6, -40, 26; Lower row: L) Right VLPFC: 50, 5, 29; M) Left precentral gyrus: -51, -17, 34; N) Right parietal lobe: 3, -67, 40; O) Right inferior parietal lobe: 33, -57, 43; P) Left SMA: -1, 6, 57; Q) Right superior parietal lobe: 33, -40, 55.

Table 4-6: Talairach coordinates of significant activity (increased or decreased activity) within the same task (NSD) across states. Values are obtained using the contrasts at session 3 minus session 1.

Brain area	Anatomy	BA area	Talairach coordinates			Denote
			X	Y	Z	
Left AFC	Middle frontal gyrus	10	-44	45	-3	A
Left VLPFC	Inferior frontal gyrus	47	-42	21	-17	B1
Right VLPFC	Inferior frontal gyrus	47	51	18	4	B2
Left SMA	Medial frontal gyrus	6	-1	-4	48	C
------	Precentral gyrus	4	-29	-10	52	D1
------	Precentral gyrus	4	28	-10	52	D2
Right Temporal cortex	Inferior temporal gyrus	37	45	-57	-3	E1
Left Temporal cortex	Inferior temporal gyrus	37	-48	-57	-3	E2
Left Temporal cortex	Superior temporal gyrus	38	-45	15	-9	F1
Right Temporal cortex	Superior temporal gyrus	38	46	4	-9	F2
Left Temporal cortex	Superior temporal gyrus	22	-52	-43	8	
Right Temporal cortex	Superior temporal gyrus	22	47	-43	8	
Right Temporal cortex	Medial temporal gyrus	37	45	-65	-3	G1
Left Temporal cortex	Medial temporal gyrus	37	-48	-55	-3	G2
Right Temporal cortex	Medial temporal gyrus	21	58	-33	4	H1
Left Temporal cortex	Medial temporal gyrus	21	-60	-33	4	H2
Right Temporal cortex	Primary auditory cortex	41	45	-28	10	I
Left Temporal cortex	Hippocampus	28	-32	-25	-17	J
Right Parietal cortex	Inferior parietal lobe	7	33	-57	43	L1
Left Parietal cortex	Inferior parietal lobe	7	-33	-57	43	L2
Left Parietal cortex	Superior parietal lobe	7	-22	-58	57	K1
Right Parietal cortex	Superior parietal lobe	7	22	-54	57	K2
------	Postcentral gyrus	3	58	-13	25	M
Left Parietal cortex	Precuneus	7	-3	-56	52	O

Session 3 minus session 1 continued						
Left ACC	Cinguli gyrus	24	-2	-14	40	N1
Left ACC	Cinguli gyrus	31	-1	-50	40	N2
Right Insular cortex	Insular	NA	34	-11	4	
Thalamus	Thalamus	NA	-18	-22	7	X1
------	Occipitofrontal fasciculus	NA	22	20	17	X2
------	Occipitofrontal fasciculus	NA	-18	-34	25	X3



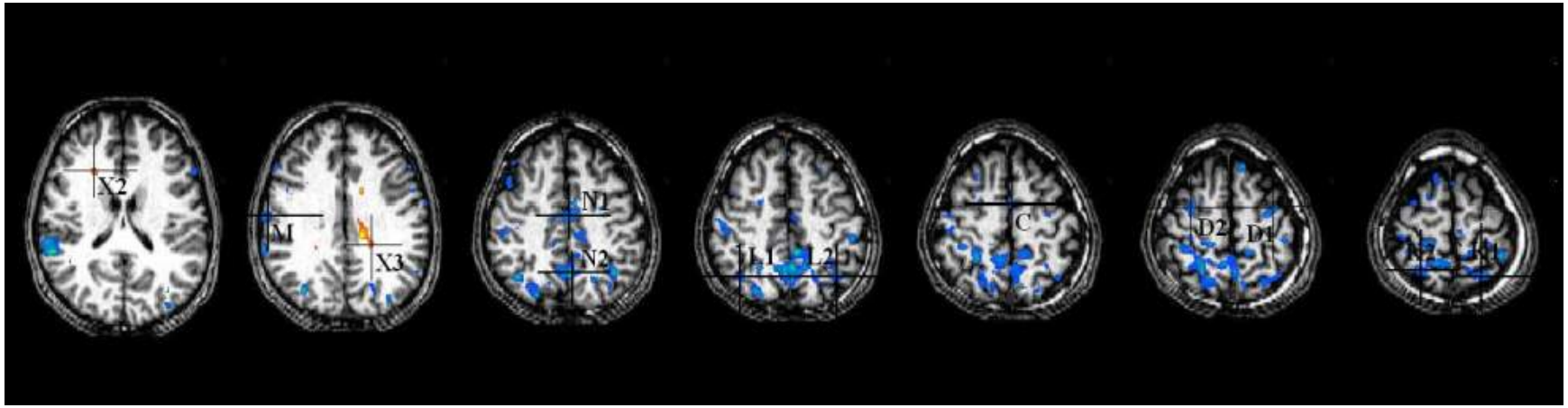


Figure 4-6: Group level activity maps observed with the contrasts session 3 minus session 1, P<0.5e-3. The Talaraich coordinates for the activity peak (indicated by cross) are as follows: upper row: B1) Left VLPFC: -42, 21, -17; J) Left hippocampus: -32, -25, -17; F1)Left

superior temporal lobe: -45, 15, -9; F2)Right superior temporal lobe 46, 4, -9; E1)Right inferior lobe: 45, -57, -3; E2)Left inferior lobe: -48, -57, -3; G1)Right medial temporal lobe: 45, -65, -3; G2)Left medial temporal lobe: -48, -55, -3; B2) Right VLPFC: -11, 17, 39; H1)Right medial temporal lobe: 58, -33, 4; H2)Left medial temporal lobe: -60, -33, 4; X1)Left thalamus: -18, -22, 7; I)Right primary auditory cortex: 45, -28, 10; Lower row: X2)Right occipitofrontal fasciculus: 22, 20, 17; M)Right postcentral gyrus: 58, -13, 25; X3)Left occipitofrontal fasciculus: -18, -34, 25; N1)Left ACC: -2, -14, 40; N2)Left ACC: -1, -50, 40; L1) Right inferior parietal lobe: 33, -57, 43; L2)Left inferior parietal lobe: -33, -57, 43; C)left SMA: -1, -4 48; D1)Left precentral gyrus: -29, -10, 52; D2)Right precentral gyrus: 28, -10, 52; K1)Left superior parietal lobe: -22, -58, 57; K2)Right superior lobe: 22, -54, 57.

Table 4-7: Talairach coordinates of significant activity (increased or decreased activity) within the same task (NSD) across states. Values are obtained using the contrasts at session 4 minus session 1

Brain area	**Anatomy**	**BA area**	**Talairach coordinates**			**Denote**
			X	Y	Z	
Left AFC	Middle frontal gyrus	10	-40	46	-8	A
Right VLPFC	Inferior frontal gyrus	47	49	24	7	B
Right DLPFC	Medial frontal gyrus	9	5	45	10	C
Left DLPFC	Medial frontal gyrus	9	-2	42	28	
------	Precentral gyrus	4	29	-30	55	D1
------	Precentral gyrus	4	41	-11	49	D2
Left Temporal cortex	Inferior temporal gyrus	37	-51	-59	-2	E
Right Temporal cortex	Superior temporal gyrus	38	40	16	-9	F1
Left Temporal cortex	Superior temporal gyrus	38	-45	15	-9	F2
Right Temporal cortex	Superior temporal gyrus	22	59	-35	7	
Left Temporal cortex	Superior temporal gyrus	22	-52	-37	7	
Session 4 minus session 1 continued						
Right Temporal lobe	Medial temporal gyrus	37	48	-52	2	G1
Left Temporal lobe	Medial temporal gyrus	37	-44	-52	2	G2

Continued with last page						
Right Temporal lobe	Hippocampus	35	21	-32	-11	H
Right Parietal lobe	Inferior parietal lobe	7	33	-62	41	I
Left Parietal lobe	Superior parietal lobe	7	-25	-76	34	J1
Right Parietal lobe	Superior parietal lobe	7	21	-68	41	J2
------	Postcentral gyrus	1	59	-16	25	
Left Parietal lobe	Precuneus	7	-3	-56	49	
Left ACC	Cinguli gyrus	31	-2	-52	41	K1
Left ACC	Cinguli gyrus	24	-2	3	28	K2
Right Insular cortex	Insular		35	-3	-5	
Right ACC	Cinguli gyrus	23	6	-21	28	X1
Left TH	Thalamus	NA	-21	-19	7	X2
Right TH	Thalamus	NA	15	-13	10	X3
Left TH	Thalamus	NA	-24	-4	7	X4
Left TH	Thalamus	NA	-16	-16	10	X5

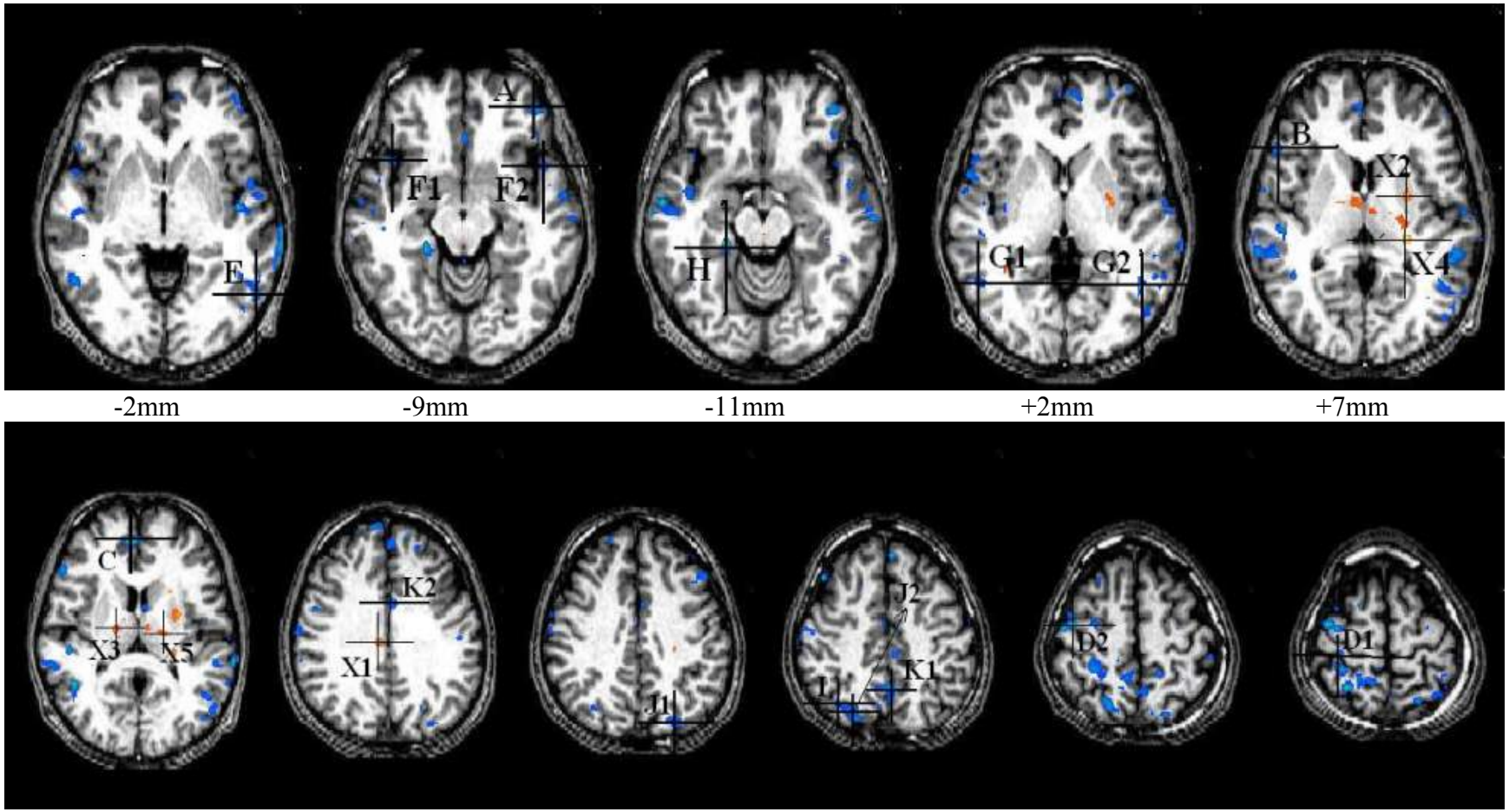


Figure 4-7: Group level activity maps observed with the contrasts session 4 minus session 1, P<0.5e-3. The Talaraich coordinates for the activity peak (indicated by cross) are as follows: upper row: E)Left inferior temporal lobe: -51, -59, -2; A)Left SMA: -40, 47, -9;

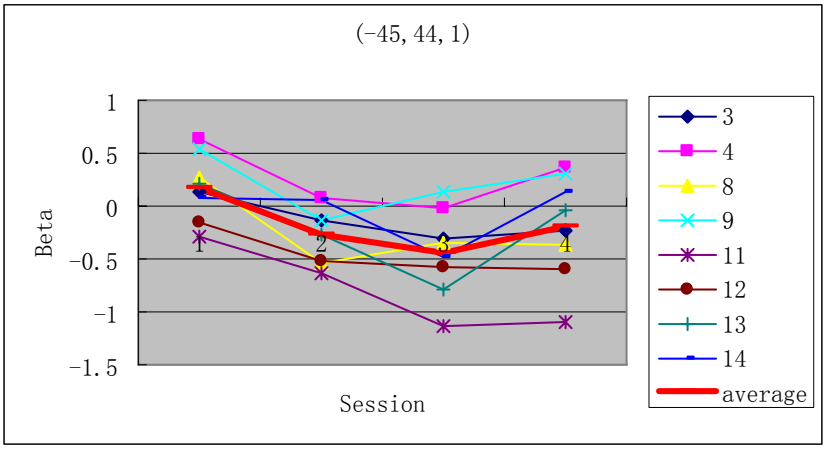
F1)Right superior temporal lobe: 40, 16, -9; F2)Left superior temporal lobe: -45, 15, -9; H)Hippocampus: 21, -32, -11; G1)Right medial temporal lobe: 48, -52, 2; G2)Left medial temporal lobe: -44, -52, 2; B)Right VLPFC: 49, 24, 7; X2)Left TH: -21, -19, 7; X4)Left TH: -24, -4, 7; Lower row: C)Right DLPFC: 5, 45, 10; X3)Right TH: 15, -13, 10; X5)Left TH: -16, -16, 10; X1)Right ACC: 6, -21,28; K2)Left ACC: -2, 3, 28; J1)Left superior parietal lobe: -25, -76, 34; I)Right inferior parietal lobe: 33, -62, 41; J2)Right superior lobe: 21, -68, 41; K1)Left ACC: -2, -52, 41; D2)Right precentral gyrus: 41, -11, -9; D1)Right precentral gyrus: 29, -30, 55.

As indicated in the equation (1), the value of β is the indication of the activation of the specific voxle of the brain image. On each circadian mental fatigue state, i.e. the session we scan the brain by fMRI, the β of the ROI was calculated. Figure 4-8 shows the plot of the β at each session across the PFC, the motor cortex (Mo), the primary auditory cortex (Au), the PL, the ACC, and the TH. The trend of the activation of all the ROI except the ACC and the TH shows the general decrease till the session 3 and later comes back at the session 4.

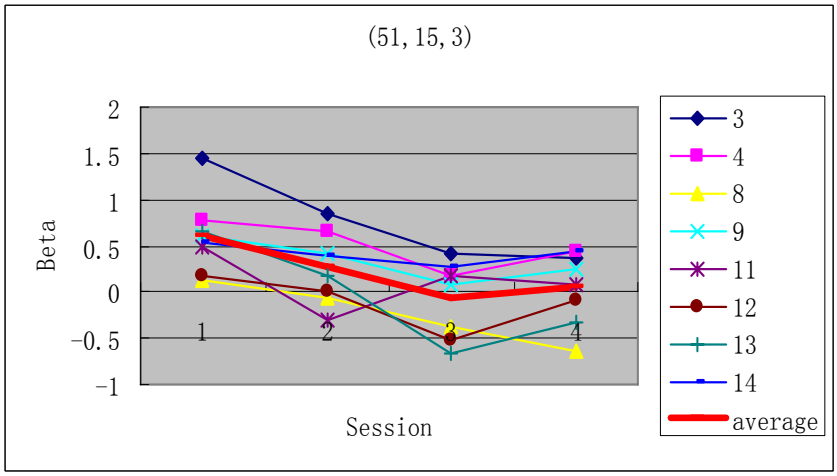
The value of the β at each session of the ROI were analyzed through the t-test which is to compare the two samples and tells the probability of the two samples with the significant difference. The results are summarized in Table 4-8.

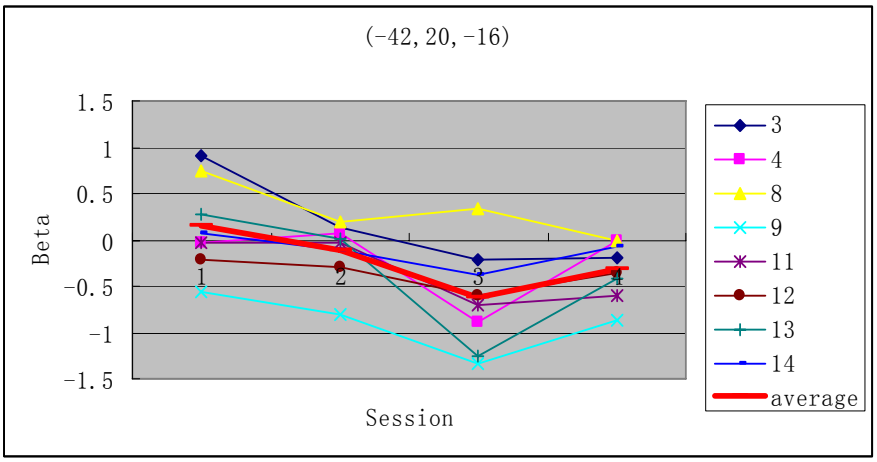
A) PFC

a) AFC

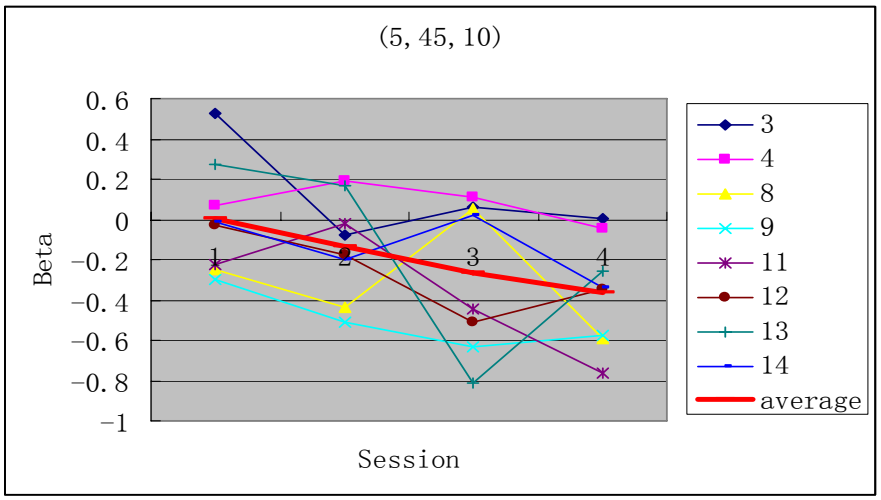


b) VLPFC

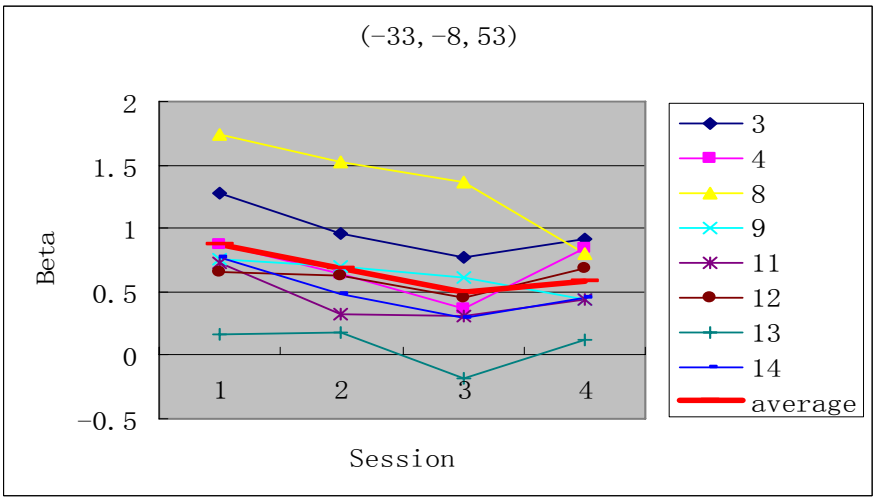




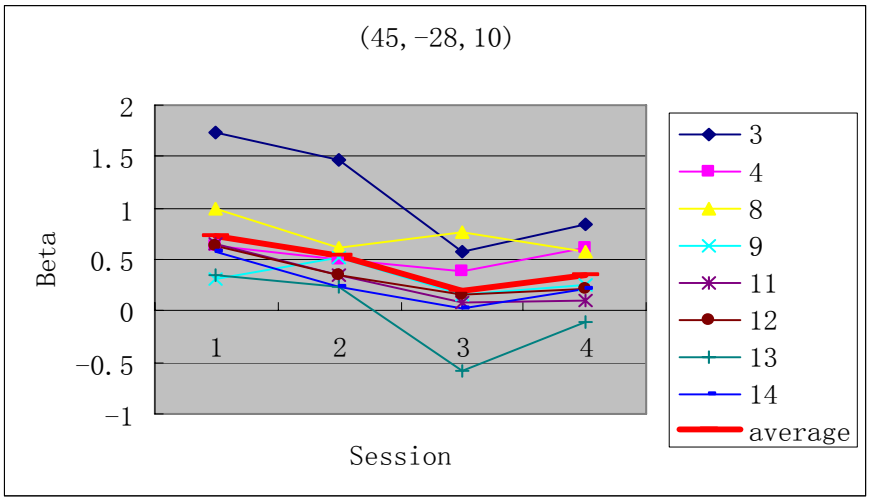
c) DLPFC



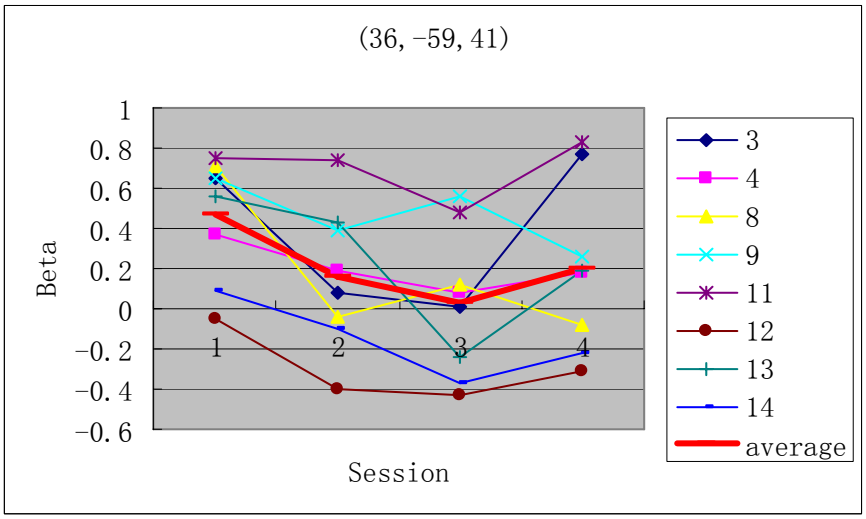
B) The motor cortex (Mo)

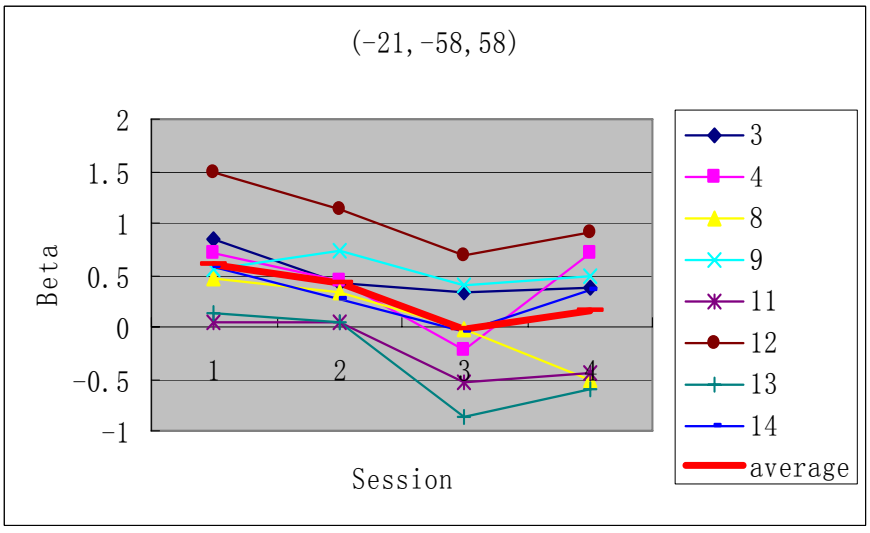


C) The primary auditory cortex(Au)

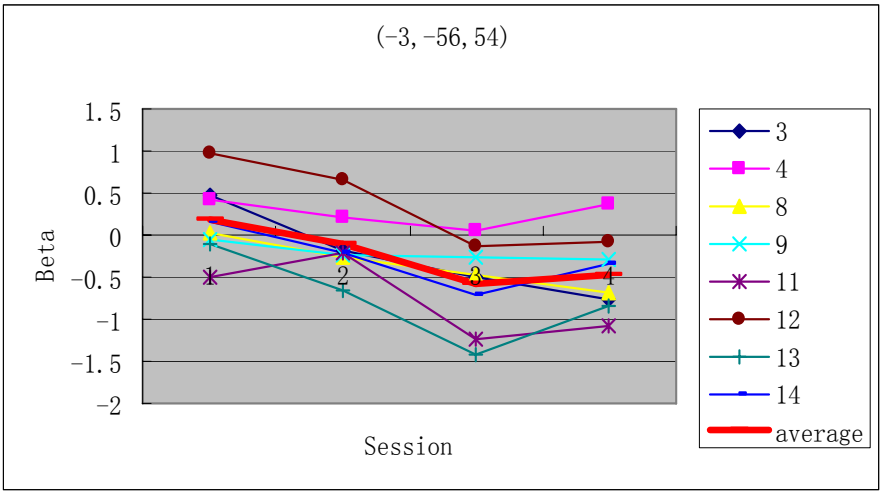


D) PL

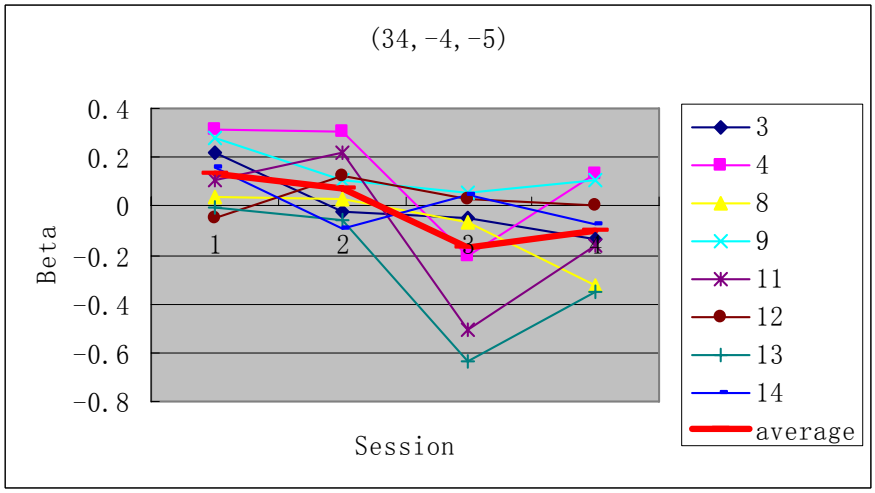




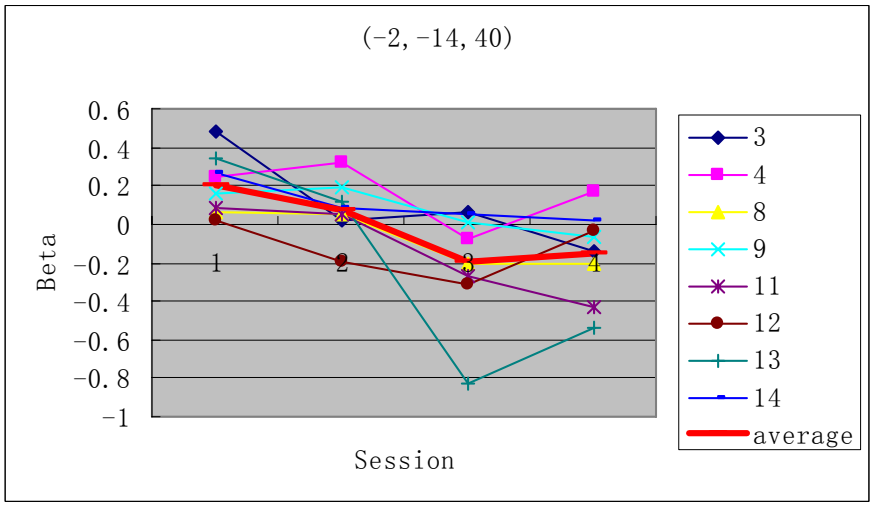
Precuneus (PCu)

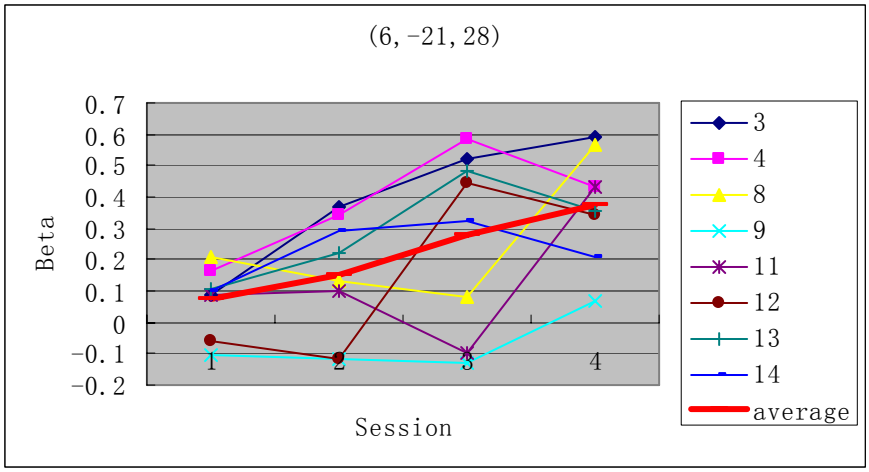


E) Insular (INS)

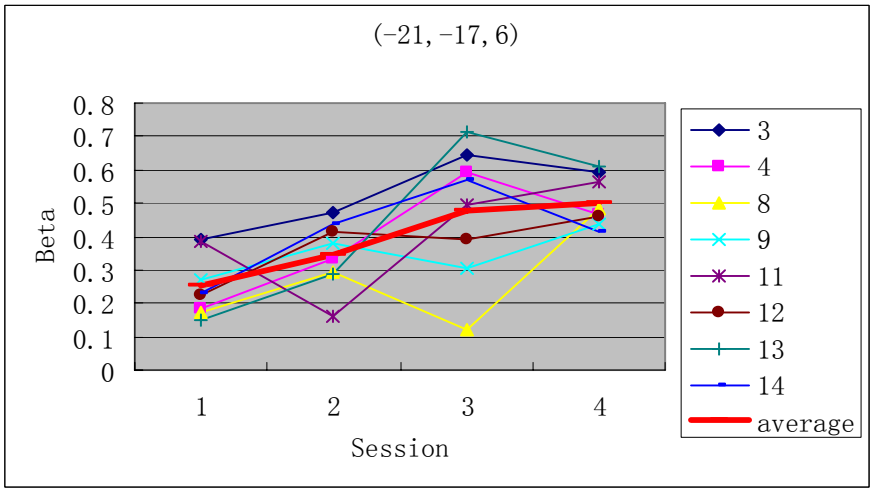


F) ACC





G) TH



H) Hi

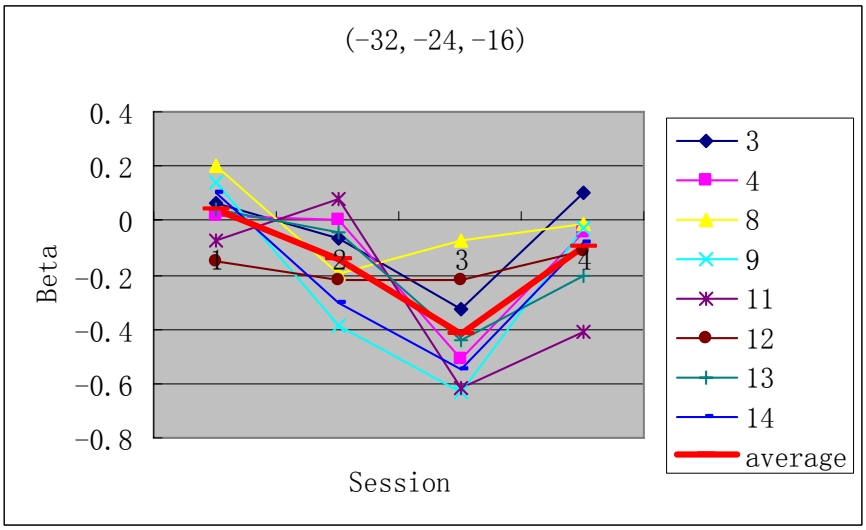


Figure 4-8: The plot of β in each session. The peak of the activation area was indicated by Talairach coordination for A) PFC: a) AFC:(-45,44,1); b) VLPFC: (51,15,3),(-42,20,-16); c) DLPFC: (5,45,10). B) The motor cortex: (-33,-8,53); C) The primary auditory cortex: (45,-28,10); D) Parietal lobe: (36,-59,41),

(-21,-58,58); Precuneus (-3,-56,54); E) Insular (Ins): (34,-4,-5); F) ACC: (-2,-14,40),(6,-21,28); G) TH: (-21,-17,6); H) Hi: (-32,-24,-16).

Table 4-8: T-test of the β of ROIs at 2 different sessions. The significant differences of two of the 4 sessions are indicated by the P value, which are in BOLD. The "*" indicates the area with increased activation across the four sessions.

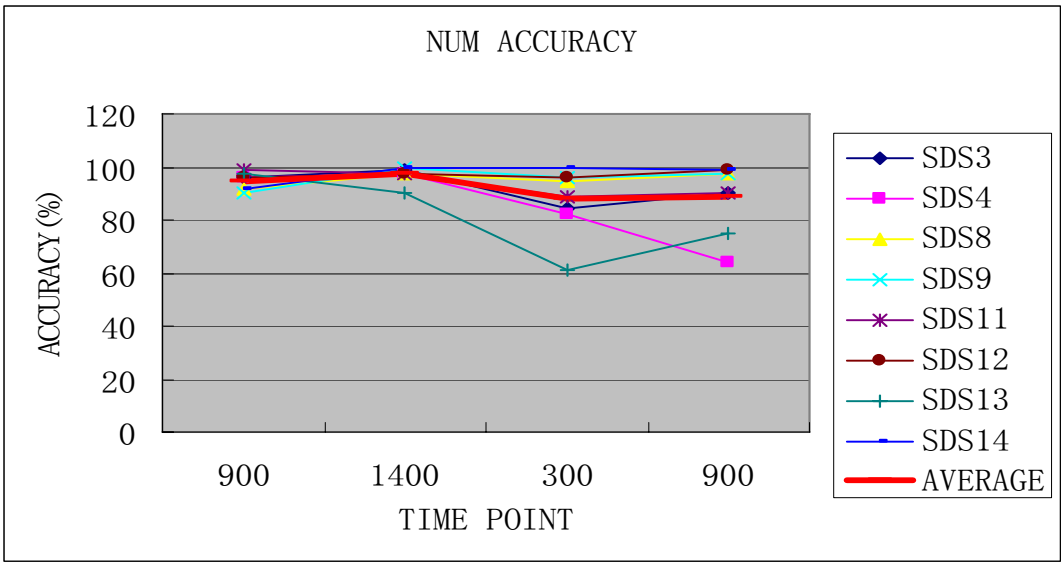
ROIs		Comparison between 2 different sessions				
Brain area	**Talairach coordinates**	**1^{st}&2^{nd}**	**2^{nd}&3^{rd}**	**1^{st}&3^{rd}**	**1^{st}&4^{th}**	**3^{rd}&4^{th}**
AFC	(-45, 44, 1)	0.01070256	0.305719	0.004167966	0.098805342	0.276815086
VLPFC	(51, 15, 3)	0.11041777	0.128685	0.00204039	0.017083135	0.560079277
VLPFC	(-42, 20,-16)	0.243993	0.036222	0.01003	0.040097	0.185769
DLPFC	(5, 45, 10)	0.316529	0.405701	0.116227	0.017929	0.567268
Mo	(-33, -8, 53)	0.401561375	0.418323	0.124883145	0.152908929	0.654143267
Au	(45,-28, 10)	0.375388865	0.116237	0.0265062	0.063958103	0.451053044
PL	(36,-59, 41)	0.085437013	0.473297	0.02037543	0.172557536	0.386283969
PL	(-21,-58, 58)	0.40963972	0.056414	0.0194892	0.113551149	0.500641537
PCu	(-3,-56, 54)	0.192544386	0.058527	0.007449294	0.014292721	0.641583565
Ins	(34, -4, -5)	0.428245176	0.03781	0.01304495	0.011064647	0.57506869
ACC	(-2,-14, 40)	0.117602515	0.0337	0.00427291	0.002800065	0.765898685
ACC*	(6,-21, 28)	0.321861043	0.322929	0.07894345	0.000919252	0.420468312
TH*	(-21,-17, 6)	0.06651612	0.11225	0.0101452	0.0000318155	0.74766098
Hi	(-32,-24,-16)	0.01859841	0.00819	0.0000518108	0.052264403	0.00271284

5 Discussion

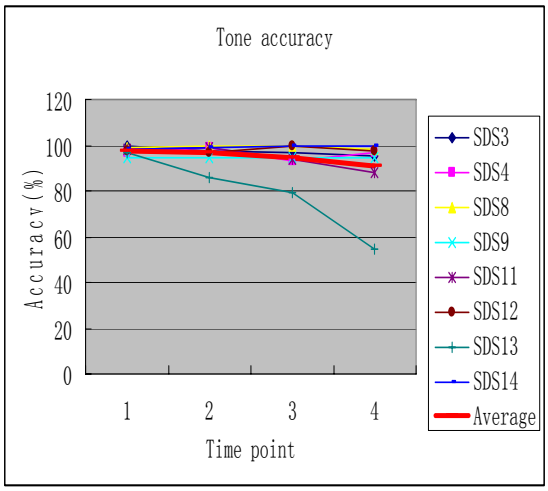
5.1 Significance in behavioral measures to be achieved by recruiting more subjects

No significant effect of state was found with regard to the behavioral data. This is likely to have arisen due to two reasons. Firstly, most subjects were exhibiting a ceiling effect with regard to accuracy. With reference to Figure 5-1 a) and Figure 5-2 b), it should be observed that most of the subjects were achieving an 85% level of accuracy under both conditions across the different fatigue states. Secondly, the lack of significance could have arisen due to the insufficient power of the data (Table 5-1).

a)



b)



c)

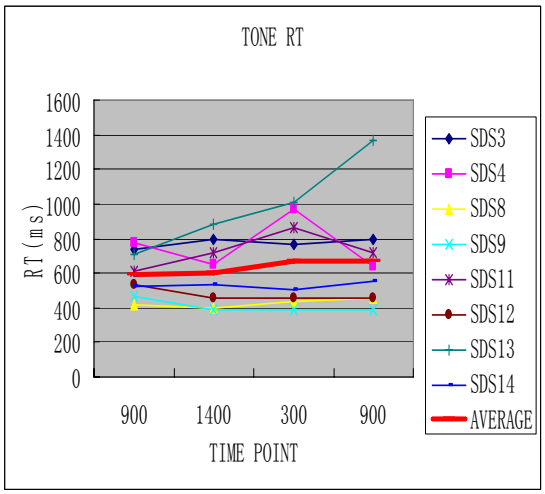


Figure 5-1: : Plots showing the individual behavioral data for both accuracy and RT with the brain activation status of specific subjects: a) Accuracy of NSD task as a function of fatigue states; b) Accuracy of TTD task as a function of fatigue states; c) RT of TTD task as a function of fatigue states

Table 5-1: Repeated measures of ANOVA with fatigue state for the 2 different discrimination task showed no main effects of the state.

Effect	NSD task accuracy	TTD task	
		Accuracy	RT
Df	3	3	3
F-value	1.94	0.99	0.27
Sig.	0.147 (n.s.)	0.413 (n.s.)	0.85 (n.s.)

n.s.: non-significant

5.2 Analysis of the 1st hypothesis: The general decreased brain activity of the brain throughout the whole circadian fatigue process.

The brain shows the general decreased activity throughout the whole circadian fatigue. As the Figure 4-4 indicates, the activation of the session 2 minus session 1, session 3 minus session 2, and session 4 minus session 3, the results shows that the minus value of the activation which indicated by the blue color. The gradually reducing the brain activation from the session 1 to the session 4 after 24 hours staying awake should be

the protecting mechanism of the brain. The parts of the brain and the organs which are supposed to join in the task are kept away from damaging after an unremitting cognitive stress.

As shown in Figure 4-8 which shows the activation across the 4 sessions during 24 hours in region of interests (ROIs), the β value went down from the first session to the third session which had the lowest and they went up in the fourth session that was held on the 2nd day at the same time as the first session. However, the β value did not get to the same states as the first session. This could be due to the effect of the circadian rhythm. After 24 hours, the brain manages to catch up the circadian effect to get to the alertness as the states at the same time 24 hours before. But the protecting mechanism drops it down. The result of the circadian fatigue is the balance of the circadian rhythm and the protecting mechanism.

Further more, as the performance of the individual shows (Figure 4-3 & Figure 5-1), the results of the brain activation and the performance give us the same trend. This is not coincident, but it is because the circadian fatigue which is reflected in the brain. As the control center of the human body, the brain affects the operating parts of the performance. It is understandable that the operating system and the control center have the same results of the circadian fatigue.

In conclusion, circadian fatigue is the states of the brain affected by the circadian rhythm. With the general decreased activity of the brain, circadian fatigue can be classified according to the different level of the brain activation based on the task. It is more scientific to classify the circadian fatigue according to the brain activation which

is essentially the neural firing of a bunch of the neurons. How to dividing the circadian fatigue states is beyond the scope of present study. But the present study proposed a new point of view to understand the circadian fatigue.

5.3 Analysis of 2nd hypothesis: There are specific parts of the brain more sensitive to the circadian fatigue.

5.3.1 More sensitivity to the circadian fatigue found in the anterior frontal cortex (AFC)

As we understand the circadian fatigue is a brain state affected by the circadian rhythm, it is curious for us to know how the brain is affected and which parts of the brain are concerned for the most.

Based on the task we designed, e.g. the number sequence discrimination (NSD task, the brain has to contribute at least 3 different areas for the out put of the performance: 1) the auditory cortex which charges the listening of the commands; 2) the area for analysis of the commands which we call the prefrontal cortex; 3) the primary motor cortex to control the finger pressing to the button. Of course, the simple pressing the button is a complex cooperation of many different areas of the brain. We just simplify the pressing model of the brain to find out which is the most sensitive area of the task primarily including areas. From the previous study by Drummond et al. (1999), we propose that the prefrontal cortex (PFC) should be much more sensitive to the circadian fatigue, i.e. PFC is in the manner of decreased activity in advance.

From the Figure 4-5, Figure 4-6, and Figure 4-7, we can find that the brain activity on each fatigue state include the ROIs we proposed and also other areas, such as the

insular, the precuneus and the Hippocampus in the temporal lobe. We can see that the activation of the primary auditory cortex (Au) (Figure 4-8 (C)), the AFC (Figure 4-8 (A)) and the motor cortex (Mo) (Figure 4-8 (B)) show the same trend of the activity across the 4 sessions. However, there are differences among them. Referred to the Table 4-8, we can see that the difference of the 2 of the 4 sessions can be indicated by the P value in the t-test. For the anterior frontal cortex (AFC), it shows the significant difference between the brain activity of the first session and the second session. After that, it is in the manner of non-significant effect from the second to the third session and from the third session to the fourth session. Compared with the activity of anterior frontal cortex (AFC), the brain activation at the Au and Mo shows the significant difference at the third session or even no much difference e.g. Mo.

This indicates that the anterior frontal cortex (AFC) reduced its activity earlier at the second session and the decreased activity continues gradually but without too much difference. On the other hand, the auditory cortex (Au) reduced its activity dramatically at later session—the third session and the decreased activity of motor cortex (Mo) just behaved gradually without big difference.

The results are perfectly coincident with our prediction. The reasons might be the protection effect of the brain from the circadian fatigue. The regions of the brain involved in the task can maintain a relatively stable performance. Thus the more sensitive region such as the AFC, has to reduce its activity to make sure the accomplishment of the task in the future. In another word, the decreased activity of the AFC saves the energy to protect the brain for further task demanding in the future hours at some early fatigue level. Another, the order of the operating area of the brain

is proposed here. The auditory cortex and the motor cortex are the areas related to the stimulus and response directly. The anterior frontal cortex (AFC) is the higher order. It has to receive the signal from the auditory and analyze the stimulus before it sends out the commands to the motor cortex to control the finger pressing. The complex functions of the anterior frontal cortex (AFC) make it using the energy and the oxygen much more. As a result, the time of the day causes it responding to this requirement, which is anterior frontal cortex (AFC) much more sensitive to the circadian fatigue.

5.3.2 Dorsolateral prefrontal cortex (DLPFC) only sensitive to the extreme fatigue states and cognitive stress

Contrary to earlier imaging studies on working memory (WM) (Braver et al., 1997; Jaeggi et al., 2003) which associated the dorsolateral prefrontal cortex (DLPFC) with little activation during low load conditions, the present study found that the simple task we designed causes continued activity until the 4th session. This has been shown in Table 4-7. The dorsolateral prefrontal cortex (DLPFC) only appeared to have the decreased activity as the result of the session 4 minus session 1. Figure 4-8 (c) shows that the activation of dorsolateral prefrontal cortex (DLPFC) at each session is smaller than the previous session. Not like the other part of prefrontal cortex (PFC), dorsolateral prefrontal cortex (DLPFC) decreased its activity further from the 3rd session significantly (Table 4-8). Increased demands on cognitive would be accompanied by increased cerebral activity (fMRI signal) as long as a certain level of performance can be maintained (Jansma et al., 2000). In this task, however, accuracy doesn't display big difference as the fatigue goes into deeper states from the session 3. In this study the dorsolateral prefrontal cortex (DLPFC) shows its manner of more and more decreased activity either because "maximum processing has been exceeded"

or because it just “fails to contribute” (Jansma et al. 2000) to the fatigue states extreme and the cognitive stress.

The continued decreased activation at each session can be attributed to its role in mediating executive functions (Cohen et al., 1997), some of which involved the regulation of the other cortical regions and the coordination of their processing (Reichle et. al., 2000). The present task required subjects to set up and keep track of goals and this involves the maintenance of information in an active state. In addition, the subject is also required to keep track of subgoals (keeping focused during the task and making sure that a response for the present stimulus is made before the next one appears) and this would entail the coding and retrieval information in time. These two processes are within the domain of “executive functions” undertaken by the DLPFC (Fletcher & Henson, 2001; Smith & Jonides, 1999). On the other hand, the PFC is anatomically connected to many cortical areas including the parietal lobe (PL) (Corbetta, 1998), cinguli gyrus (ACC) (Devinsky et al., 1995), thalamus (TH) (Kubat-Silman, 2002), insular cortex (INS) (Augustine, 1996), to name a few. Following up on the earlier postulation that the maximum processing “power” of the dorsolateral prefrontal cortex (DLPFC) could have been exceeded in the present task, the decreased activity of the dorsolateral prefrontal cortex (DLPFC) following SD could reflect a protection response. To following the effects of the “deficit” brought about by the fatigue, the dorsolateral prefrontal cortex (DLPFC) could reduce its modulatory inputs to the other cortical areas in which it is connected, for example, the thalamus and the cinguli gyrus, and thus causing these parts signals to increase consequently (Figure 4-8).

5.3.3 The cognitive impairment induced as a result of circadian fatigue is accompanied by parietal lobe (PL) related to the working memory.

In another study conducted by Drummond et al. (1999), activity in the prefrontal cortex (PFC) and parietal lobe (PL) was reduced following 24 hours staying awake. On the other hand, the parietal lobe (PL) is anatomically connected to many cortical areas including the PFC (Corbetta, 1998). At the present study, the same trend is postulated.

A study by McCarthy & Waters (1997) has shown that sleep debt not only decreases the attentional responsivity of subjects to new information, but also reduces their efficiency of cognitive processing. As such, the human brain after one sleepless night is clearly functioning on a lower level at all times (Gillberg & Akerstedt, 1998). This would thus imply a decreased ability of the brain during the sleep deficit state to perform. The decreased activation of the parietal lobe (PL) (inferior and superior) took the same results as the performance accuracy. As the cognitive awareness went down accompanying with the fatigue, the results of the cognitive performance reflect the low level of the cognitive processing of the higher order including parietal lobe (PL).

Involvement of frontal-parietal network in fatigue is proposed here. The left PL has been known to be involved in the phonological storage of verbal WM (Paulesu *et al.*, 1993). In the NSD task, the commands were phonological. Thus, the decreased activity following circadian fatigue would suggest the fatigue effects across the PL. The frontal areas have been found to be involved across the whole fatigue process, thus implying its necessary involvement in the task. There was also an activation of

Broca's area (left BA 44) and the parietal lobe (BA 40). As these two areas are involved in the phonological storage of working memory, they are likely to play an important role in the 'articulatory loop' of working memory (Paulesu et al., 1993). In addition, the supplementary motor area (SMA) (BA 6) found to be involved with the circadian fatigue (Table 4-5 & Table 4-6), have been proposed by Braver et al (1997) to be associated with Broca's area in mediating subvocal articulatory processes such as verbal rehearsal. The involvement of a network of cortical areas involved in working memory are consistent with Jaeggi et al. (2003)'s findings, and appears to support the working memory model proposed by Baddeley (1992) in which the Broca's area, together with the inferior parietal lobe, the supplementary motor cortex and the frontal lobes each assume specific processes within their cortical domains.

5.4 Analysis for the 3rd hypothesis: Cinguli Gyrus (ACC) and Thalamus (TH) effect of the circadian fatigue

The Cinguli Gyrus (ACC) has been implicated in mediating arousal (Jansma et al., 2000), while the Thalamus (TH) has been found to be involved in mediating attention (Portas et al., 1998). Since SD results in reduced vigilance (Binks et al., 1999) and lowered arousal (McCarthy & Waters, 1997), the subjects would need to counteract these physiological responses by compelling themselves to not only stay awake, but also complete the task. All subjects were informed before-hand that payment would only be administered following the successful completion of the task. As such, the monetary motivation to stay awake could have resulted in increased activation in Cinguli Gyrus (ACC) and Thalamus (TH).

5.4.1 Role of Cinguli Gyrus (ACC) in serving attention control

As indicated in Figure 4-8 (F) & (G), Cinguli Gyrus (ACC)and Thalamus (Th) are the special parts of the brain under the effect of the circadian fatigue. Although most of the part of the brain took the manner of the decreased activity across the four sessions, Cinguli Gyrus (ACC) and Thalamus (Th) showed their specialty with more and more activation at each session throughout the fatigue. The present findings have largely abided to as that hypothesized, with the ACC and thalamus showing greater activation in fatigue states.

The present study reveals an increased activation of the ACC following the circadian fatigue. This reinforces its proposed role in response monitoring (Badgaiyan & Posner, 1998). A study conducted by Carter et al. (2000) had found the Cinguli Gyrus (ACC) to be responsible for evaluating processing conflicts that may result in behavioral performance decline. As such, an increased activation of Cinguli Gyrus (ACC) would thus reflect the enhanced sensitivity to errors. In addition, Cinguli Gyrus (ACC) activations have been shown to reflect "cognitively demanding information processing (Devinsky et al., 1995). In the above-mentioned condition, the 'cognitive stress' induced as a consequence of fatigue would thus result in an increase in the likelihood of a blunder during the task. The intensified alertness thus activates the Cinguli Gyrus (ACC), a component in the "error prevention" network, to a greater extent. On the other hand, the increased activation of the Cinguli Gyrus (ACC) could be due to feedback from the thalamus. This is in accordance with the proposed model by Frith & Friston (1996) in which the thalamus is responsible for binding together the features of attention by initiating a signal which is then used to synchronize firing

in the different cortical areas, one of them of which would be the Cinguli Gyrus (ACC).

The engagement of the Cinguli Gyrus (ACC) following increased cognitive stress can also be accounted in terms of the existing prefrontal-cingulate interactions. The Cinguli Gyrus (ACC) and Thalamus (Th) have been found to play distinct yet complementary roles in the neural network serving attentional control (Gehring & Knight, 2000; MacDonald et al., 2000). The dorsolateral prefrontal cortex (DLPFC) has been suggested to be involved in the representation and maintenance of the attentional task demands while the Cinguli Gyrus (ACC) plays a role in conflict monitoring (MacDonald et al., 2000). This role of the Cinguli Gyrus (ACC) in mediating executive control is analogous to a "central executive" (Casey et al., 2000), and is therefore likely to be made possible by the engagement of the dorsolateral frontal cortex.

5.4.2 Role of Thalamus (TH) in mediating attention

The thalamus is yet another structure consistently activated across the circadian fatigue. As noted by Frith & Friston (1996), an increase in thalamic activity has been found across a few studies employing attention demanding tasks. Also, the thalamus has been suggested to assume a chief role in selective attention (LaBerge, 1995), which basically refers to the mental ability to select stimuli, responses, or thoughts that are behaviorally relevant amidst the many others that are behaviorally inapplicable (Corbetta, 1998). This therefore suggests that its recruitment in the present study could have been necessary as subjects focus their attention to execute the correct response with regard to each of the stimuli. On the other hand, thalamic in

facts have been commonly associated with prefrontal executive function impairments (Kubat-Silman et al., 2002). In addition, the thalamus is anatomically interconnected to the prefrontal cortex as the mediodorsal nucleus, anterior nucleus, and ventrolateral nucleus of the thalamus all have frontal lobe connections (Kubat-Silman et al., 2002). This close association between the thalamus and the prefrontal areas could mean that the thalamus could have been activated following a modulatory input by the prefrontal areas in response to task activation.

5.5 Analysis for the 4th hypothesis: The auxiliary brain regions searched following the circadian fatigue progresses

Following the reduction in signal in the prefrontal cortex (Drummond et al., 1999), it is likely that additional brain areas will be recruited so as to compensate for the effects brought about by the decreased activity of the prefrontal cortex.

Comparing across the states at the different fatigue level to that in the first session, the present findings failed to detect the activation of any auxiliary areas following sleep debt. This suggests that, in contrary to the hypothesis, the effects of sleep deprivation are not manifested in the recruitment of additional areas to mediate the 'stress' incurred as a result of the fatigue. In view of the concluded findings thus far, it is likely that the brain compensates for the effects of fatigue by manipulating the activation status of the areas already implicated in the task instead of recruiting additional areas to rectify the cognitive stress.

5.6 Significance in recruitment of the Insular (INS) to mediate cognitive processes under the fatigue states

The insular which is not the region of interests was also found to have the same decreased activity across the four sessions (Table 4-5, Table 4-6 & Table 4-7), thus suggesting its essential role in fatigue functions. While it has been found to play an integral role with regard to human physiological functioning, it also has a role mediating cognitive functions (Augustine, 1996). In a study conducted by Paulesu et al. (1993), the insular was found to be bilaterally activated in the performance of a rhyming judgment task. This, Paulesu et al. thus suggests, implicates the insular in the "functional anatomy of the 'articulatory loop'". In addition, the insular has also been found to be involved in mediating selective attention (Corbetta et al., 1991). These functions could be fostered by the close anatomical connections of the insular lobe to the regions of the cerebral cortex, some of which include the frontal lobes, the temporal lobes, the cingulate cortex and the dorsal thalamus in primates.

5.7 Sensitivity of the Precuneus (PCu) and Hippocampus (Hi) to memory

The precuneus and hippocampus, the regions not designated as an region of interest, were found to exhibit decreased activity across the four sessions also (Table 4-5, Table 4-6 & Table 4-7). The precuneus, a medial parietal brain region, is situated superior and posterior to the retrosplenial area of the cingulate cortex and has been postulated to play an integral role in task-elicited awareness together with the prefrontal regions (Kjaer et al., 2001). As such, its decreased activity in the presence of the four sessions could reflect a channeling of decreased attentional resources, as subjects became less "aware" while performing the task as a result of lower performance accuracy. On the other hand, another proposed function of the precuneus

is that its serves as an important “neural substrate of visual imagery occurring in conscious memory recall” by subserving the function of a visual imagery buffer through its activation (Fletcher et al., 1995). As such, the decreased activity following deeper and deeper fatigue could therefore imply the less and less use for the memory and visual imagery, as the subjects were going through the extreme fatigue which is sleep. The record of the performance could tell us the subjects were not asleep.

The hippocampus is known for its function of long term and short term memory. As such, it presented the sensibility to the fatigue throughout the four sessions (Figure 4-5). As indicated in the Figure 4-8 (H), it reduced its activity sharply from the first session to the second session, and to the third session. Affected by the circadian rhythm, after the fatigue extreme on the session 3, it recovered from the low activity on the fourth session. The activation differences between each session to the first are significant (Table 4-8). This implies that the circadian fatigue influence the memory process largely. One of the reasons should be the shutting down of hippocampus can make the brain focus on management of the central cognitive control of performance. Another, we can conclude that it is influence by the circadian rhythm directly other than controlled by the higher order of cognitive engaged areas we discussed above.

6 Conclusion and Recommendation for Future Work

6.1 Conclusions

In the present study, we proposed four hypothesis of the brain activity under the circadian fatigue. We are able to draw following conclusions based on the results of the present study.

6.1.1 The general decreased activity of the cortex throughout the fatigue process.

The subtraction of the later session from the previous session indicates the decreased activity throughout the 4 sessions in 24 hours. Because of the restlessness within 24 hours, the brain managed to catch up the circadian effect to get to the alertness the same as the states at the same time 24 hours before. But the protecting mechanism dropped it down. The result of the circadian fatigue should be the balance of the circadian rhythm and the protecting mechanism.

6.1.2 There are some specific parts of the brain which are sensitive to the circadian fatigue

The decreased activity was found in the anterior frontal cortex (AFC), dorsolateral prefrontal cortex (DLPFC) and parietal lobe (PL).

1. For the anterior frontal cortex (AFC), it is more sensitive to the circadian fatigue. A sensitive decreased activation was observed across four sessions in anterior frontal cortex. The reasons might be the consequence of the circadian fatigue. The frontal and parietal lobes could possibly function as a

neurophysiological substrate of the initial protection for the effects of rest debt in order to maintain partially intact performance in the later hours. Another, the anterior frontal cortex is the higher order. It has to receive the signal from the auditory and analysis the stimulus before it sends out the commands to the motor cortex to control the finger pressing. The complex functions of the anterior frontal cortex make it consuming the energy and the oxygen much more than others. As a result, the time of the day causes it responding to this requirement, which is anterior frontal cortex much more sensitive to the circadian fatigue.

2. The dorsolateral prefrontal cortex (DLPFC) is only sensitive in the fatigue extreme and cognitive stress. Dorsolateral prefrontal cortex which mediates both attention and arousal after fatigue in order to maintain intact performance also showed continues decreased activity as a consequence. The sensitivity in the fatigue extreme can be attributed to its role in mediating executive functions. Another, the prefrontal cortex is anatomically connected to many cortical areas including the PL, Cinguli Gyrus (ACC), Thalamus (TH), insular cortex (INS) etc. To protect the brain from the effects of the "deficit" brought about by the fatigue, the dorsolateral prefrontal cortex could reduce its modulatory inputs to the other cortical areas in which it is connected. The modulatory inputs exerted by the dorsolateral prefrontal cortex responses to excessive processing demands.
3. The parietal lobe (PL) is accompanied by the fatigue induced cognitive impairment. An equivalent activity was observed in the superior parietal lobe as well as the inferior parietal lobe. The parietal lobe has been known to be involved in the phonological storage of verbal working memory (WM) and

the parietal lobe is anatomically connected to many cortical areas including the prefrontal cortex. In the network of frontal-parietal due to fatigue, the commands of the present task are phonological. Thus, the decreased activity following circadian fatigue would suggest the fatigue effects across the parietal lobe.

6.1.3 Cinguli Gyrus (ACC) and Thalamus (TH) effect of the circadian fatigue.

Results from the present study show that the circadian mental fatigue caused more activated in the cinguli gyrus and the thalamus following the circadian fatigue extreme.

1. The cinguli gyrus serves the attention control in the fatigue brain. The increased activation would reflect the enhanced sensitivity to errors. The intensified alertness thus activates the cinguli gyrus, a component in the "error prevention" network, to a greater extent. Another, the increased activation of the cinguli gyrus could be due to feedback from the thalamus. The thalamus is responsible for binding together the features of attention by initiating a signal which is then used to synchronize firing in the different cortical areas, one of them of which would be the cinguli gyrus. Lastly, the cinguli gyrus and prefrontal cortex have been found to play distinct yet complementary roles in the neural network serving attention control. The Dosolateral prefrontal cortex (DLPFC) has been suggested to be involved in the representation and maintenance of the attention task demands while the Cinguli gyrus plays a role in conflict monitoring.
2. Thalamus (TH) serves to mediate the attention in the fatigue brain. The thalamus has been suggested to assume a chief role in selective attention.

Thalamic in facts have been commonly associated with prefrontal executive function impairments. The close association between the thalamus and the prefrontal areas could mean that the thalamus could have been activated following a modulatory input by the prefrontal areas in response to task activation.

6.1.4 The brain does not responds to circadian fatigue by recruiting auxiliary area of the brain

We hypothesized there should be the auxiliary brain regions searched following the circadian fatigue progresses. However, the present study did not show much clues about this searching during the fatigue progress. This might be that the brain compensates for the effects of circadian fatigue by manipulating the activation status of the areas already implicated in cognition instead of recruiting additional areas to rectify the cognitive stress.

6.1.5 The brain searches the insular to mediate cognitive processes under the fatigue states

In the present study, the insular cortex which is not designed to be the ROIs was another area found to be involved in the circadian fatigue. Insular functions in the role in the "functional anatomy of the 'articulatory loop'". It has also been found to be involved in mediating selective attention. The close anatomical connections of the insula lobe to the regions of the cerebral cortex showed its importance in the fatigue states.

6.1.6 Precuneus (PCu) & Hippocampus (Hi) show sensitivity to circadian fatigue

Lastly, the precuneus and hippocampus, the regions not designated as an ROI, were found to exhibit decreased activity.

1. For the precuneus, it is situated superior and posterior to the retrosplenial area of the cingulate cortex and has been postulated to play an integral role in task-elicited awareness together with the prefrontal regions. Its decreased activity could reflect a channeling of decreased attentional resources, as subjects become less "aware" while performing the task as a result of lower performance accuracy.
2. For the hippocampus, the decreased activity implies that the circadian fatigue influence the memory process largely. One of the reasons should be the shutting down of hippocampus can make the brain focus on management of the central cognitive control of performance. Another, we can conclude that it is influence by the circadian rhythm directly other than controlled by the higher order of cognitive engaged areas we discussed above

6.1.7 Conclusion of the effects of circadian fatigue in brain

As mentioned above, throughout the 24-hour track of the brain, the significance of the different fMRI signal changes in various regions of the brain specify the circadian rhythm effect on the brain. The overall decreased activity of the brain provides the general background of the brain activity to the circadian rhythm. The specific effect of circadian fatigue is as shown in the Figure 6.1.

1) AFC, PL, PCu, INS, Hi decrease their activities in the circadian fatigue through 24 hours sleep deprived process.

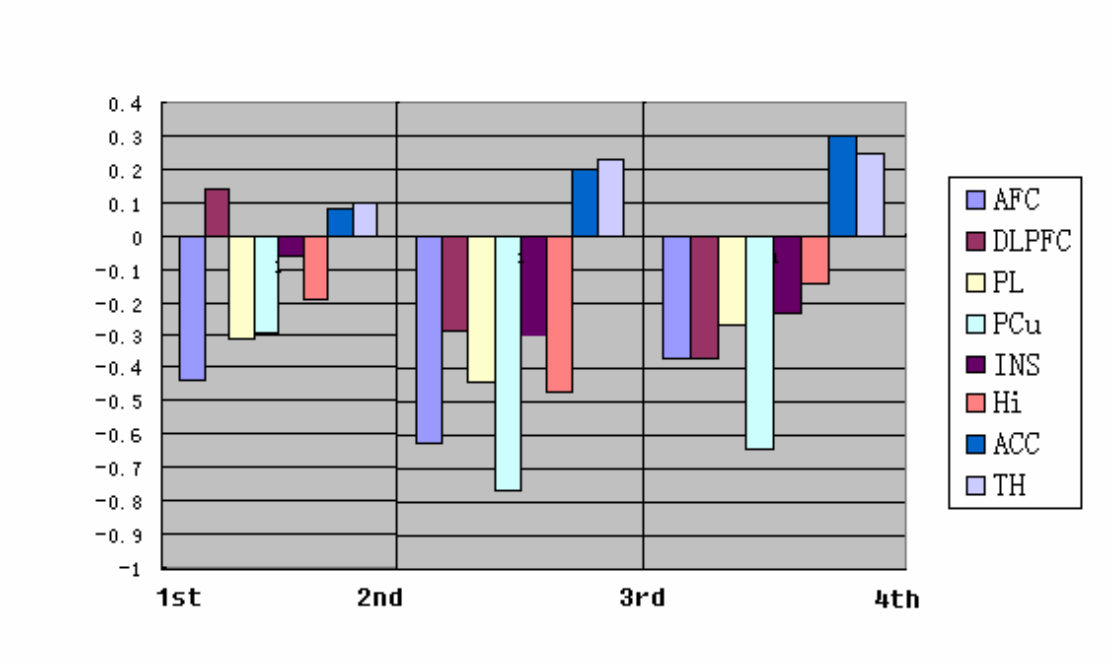


Figure 6-1: Integrated representation of activities in different brain regions throughout the process of circadian fatigue

2) DLPFC decreases slower than the other regions in interests, which shows its lowest activity level at the most fatigue state.

3) ACC and TH indicate more and more powerful activities due to the circadian fatigue.

6.2 Recommendation for future works

1. The present study has sought to elucidate the effects of circadian rhythm on brain activity at each fatigue states. However, due to the small sample, the data collected constitute only a preliminary finding as to how circadian fatigue affects cognitive performance and the neural activity of the parts of the brain involved in the cognitive task. A follow-up involving a larger sample (where n = at least 20) is likely to lead to more conclusive results.
2. To date, there are still a lot of unknowns regarding how brain mediates cognitive processing to the circadian fatigue. While extensive studies have

been conducted within this domain, the emphasis has been on fatigue states extreme after sleep deprivation, and is insufficient for us to place a judgment on the effects of circadian fatigue to the neural firing states per se.

3. The effects of the circadian fatigue are based on the specific tasks, and thus are not conclusive as yet. Hence, a possible follow-up from the current study could involve variations of tasks in which spatial and object are used as stimuli. Having then a better knowledge on how circadian influence the brain neural activity, a greater understanding on how neural firing states affect cognition can be facilitated and this may perhaps, provide a piece to the puzzle as to why circadian fatigue is important, at least with regard to cognition.

REFERENCE

Aoki, C., Milner, T.A., Berger, S.B., Sheu, K.F., Blass, J.P., and Pickel, V.M. (1987). Glial glutamate dehydrogenase: ultrastructural localization and regional distribution in relation to the mitochondrial enzyme, cytochrome oxidase. Journal of Neuroscience Research, 18, 305-18.

Baddeley, A.D. (1992) Working memory. *Science* **255**, 556-559

Bartlett, F.R.S (1953). Psychological criteria of fatigue. In W.F. Floyd & A.T. Welford (eds.), Symposium on fatigue. London: H.K.Lewis.

Bechtereva, N.P (1981). Neurophysiological Correlates of Mental Processes in Man. Psychophysiology Today and Tomorrow (Bechtereva, N.P., editor), Pergamon Press, New York, NY,.

Belyavin, A & Wright, N. (1987). Changes in electrical activity of the brain with vigilance. Electroencep. clin. neurophy 66, 137-44

Berger, R.J. & Philips, N.H. (1995) Energy conservation and Sleep. *Behav. Brain Res.* **69**, 65-73

Binks, P.G., Waters, W.F., Hurry, M. (1999) Short-term total sleep deprivations does not selectively impair higher cortical functioning. *Sleep* **22**, 328-334

Borowsky, I.W. and Collins, R.C. (1989). Metabolic anatomy of brain: A comparison of regional capillary density, glucose metabolism, and enzyme activities. Journal of Comparative Neurology, 288, 401-13.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J. Smith, E.E. & Noll, D.C. (1997) A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* **5**, 49-62

Broadbent, D.E. (1979). Is a fatigue test possible now? The Society Lecture 1979. Ergonimics, 12, 1277-1290.

Brookhius, K. A. and Waard, D. (1993) The use of psychophysiology to assess driver status," *Ergonomics*, Vol. 36, pp. 1099-1110,.

Brown, C.C. (1967) Methods in Psychophysiology, The Williams andWilkins Company, Baltimore, Maryland,

Buxton, R.B. and Frank, L.R. (1997). A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. Journal of Cerebral Blood Flow and Metabolism, 17, 64-72.

Cabeza, R, Nyberg, L. (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. *Jour. Cogn. Neurosci*. **12**, 1-47

Cameron, C (1973). “A theory of fatigue” Ergonomics. Vol. 16, No. 5.

Carter, C.S., Macdonald, A.M., Botvinick, M., Ross, L.L., Stenger, A., Noll, D. & Cohen, J.D. (2000) Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proc. Natl. Acad. Sci.* **97**, 1944-1948

Casey, B.J., Thomas, K.M., Welsh, T.F., Badgaiyan, R.D., Eccard, C.H., Jennings, J.R., & Crone, E.A. (2000) Dissociation of response conflict, attentional selection and expectancy with functional magnetic resonance imaging. *Proc. Natl Acad Sci.* **97**, 8728-8733

Cohen, J.D., Perlstein, W.M., Braver, T.S., Nystrom, L.E., Noll, D.C., Jonides, J., Smith, E.E. (1997) Temporal dynamics of brain activation during a working memory task. *Nature* **386**, 6

Conte, S., Ferlazzo, F., Renzi, (1995). Ultradian rhythms of reaction times in performance in vigilance tasks. Biol. Psychol. 39, 59-172

Corbetta, M. (1998) Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proc Natl Acad Sci.* **95**, 831-838

Devinsky, O., Morrell, M.J., & Vogt, B.A. (1995) Contributions of anterior cingulate cortex to behaviour. *Brain* **118**, 279-306

Dinges, D. F. (1995) An overview of sleepiness and accidents, *Journal of Sleep Research*, Vol. 4, Supplement 2, pp. 4-14,.

Dinges, D. F. (1989) The nature of sleepiness: Cause, contexts and consequences, *Perspectives in Behavioral Medicine: Eating, Sleeping and Sex*, Lawrence Erlbaum, Hillsdale,.

Drummond, S.P.A., Brown, G.G., Stricker, J.L. Buxton, R.B., Wong, E.C. & Gillin, J.C. (1999) Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *Neuroreport* **10**, 3745-3748

Drummond, S.P.A., Brown, G.G., Gillin, J.C., Stricker, J.L., Wong, E.C. & Buxton, R.B. (2000) Altered brain response to verbal learning following sleep deprivation. *Nature* **403**, 655-657

Ducan, G..E., Stumpf, W.E., and Pilgrim, C. (1987). Cerevral metabolic mapping at the cellular level with dry-mount autoradiography of [3H]2-deoxyglucose. Brain Research, 401, 43-9.

Duncan, G.E. and Stumpf, W.E. (1991). Brain activity patterns: assessment by high resolution autoradiographic imaging of radiolabeled 2-deoxyglucose and glucose uptake. Progress in Neurobiology, 37, 365-82.

Eisenberg, H.M., Kadekaro, M., Freeman, S., and Terrell, M.L. (1993). Metabolism in the globus pallidus after fetal implants in rats with nigral lesions. Journal of Neurosurgery, 78, 83-9.

Fletcher, P.C., Frith, C.D., Baker, S.C., Shallice, T., Frackowiak, R.S.J., & Dolan, R.J. (1995) The mind's eye—Precuneus activation in memory-related imagery. *Neuroimage* **2**, 195-200

Fletcher, P.C., & Henson, R.N.A. (2001) Frontal lobes and human memory: Insights from functional neuroimaging. *Brain* **124**, 849-881

Frith, C.D. & Friston, K.J. (1996) The role of the thalamus in "top down" modulation of attention to sound. *Neuroimage* **4**, 210-215

Gais, S., Plihal, W., Wagner, U., Born, J. (2000) Early sleep triggers memory for early visual discrimination skills. *Nature Neurosci*. **3**, 1335-1339

Gardner, E. (1975) Fundamentals of neurology, W.B. Saunders Co., Philadelphia,

Gehring, W.J., & Knight, R.T. (2000) Prefrontal-cingulate interactions in action monitoring. *Nature Neurosci.* **3**, 516-520

Gillberg, M. & Akerstedt, T. (1998) Sleep loss and performance: No "safe" duration of a monotonous task. *Physiol. Behav.* **64**, 599-604

Gonzalez-Lima, F. and Jones, D. (1994). Quantitative mapping of cytochrome oxidase activity in the central auditory system of the gerbil: a study with calibrated activity standards and metal-intensified histochemistry. Brain Research, 660, 34-49.

Gogolitsin, Y.L., Kroptov, Y.D. (1981) Application of the post-stimulus-time histogram to the analysis of discharge intellectural-M nestic activity. Psychophysiology today and Tomorrow (Bechtereva, N.p., editor), Pergamon Press, New York, NY,.

Grandjean, E. (1981) Fitting the Task to the Man. London: Taylor & Francis.

Harrison, Y. & Horne, J.A. (1997) Sleep deprivation affects speech. *Sleep* **20**, 871-877

Hartley, L.R. & Arnold, P.K. (1995). Subjective and objective measures of fatigue when driving. Report Number 109; Institute for Research in Safety and Transport.

Hartley, L., Horberry, T., and Mabbott, N. (2000). Review of fatigue detection and prediction technologies, National Road Transport Commission, Virginia, USA.

Hashemi, R.H. and Bradley, W.G. (1997). MRI: the basics. Williams and Wilkins.

Holding, D.H. (1983). Fatigue. In G.R.J. Hockey (ed.) Stress and fatigue in human performance. New York: Wiley.

Holloway, R.J. Baddely, A. D. (1976) Verbal reasoning and working memory. Quarterly Hournal of Experimental Psychology, N0. 28,

Howarth, N.L., Hefferman, C.J. & Horne, E.J. (1989). Fatigue in truck accidents. Monash University Accident Research Centre Technical Report NO. 3, Melbourne: Monash University Accident Research Center.

Howarth, N. L. & Rechnitzer, G. (1993). Description of fatal crashes involving various causal variables. Technical report CR 1, Canberra: Federal Office of Road Safety.

Idogawa, K. (1991) One the brain wave activity of professional drivers during monotonous work. *Behaviourmetrika*, Vol. 30, pp. 23-34.

Jaeggi, S.M., Seewer, R., Nirkko, A.C., Eckstein, D., Schroth, G., Groner, R., & Gutbrod, K. (2003) Does excessive memory load attenuate activation in the prefrontal cortex? Load-dependent processing in single and dual tasks: functional magnetic resonance imaging study. *Neuroimage* **19**, 210-225

Jancke, L., Shah, N.J., Posse, S., Grosse-ryuken, M & Muller-gartner, H.W. (1998). Intensity coding of auditory stimuli: an fMRI study, N*europsychologia.* **36**, 875-883

Jansma, J.M., Ramsey, N.F., Coppola, R., Kahn, R.S. (2000) Specific versus nonspecific brain activity in a parametric *N*-back task. *Neuroimage* **12**, 688-697

Jonides, J., Schumacher, E.H., Smith, E.E., Koeppe, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., Willis, C.R. (1999) The role of parietal cortex in verbal working memory. *Jour Neurosci.* **18**, 5026-5034

Karni, A., Tanne, D., Rubenstein, S., Askenasy, J.J.M., Sagi, D. (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. *Science* **265**, 679-682

Kecklund, G. and Åkerstedt, T. (1993) Sleepiness in long distance truck driving: An ambulatory EEG study of night driving, *Ergonomics*, Vol. 36, pp. 1007-1017.

Kjaer, T.W., Nowak, M., Kjaer, K.W., Lou, A.R., & Lou, H.C. (2001) Precuneus-prefrontal activity during awareness of visual verbal stimuli. *Consciousness. Cogn.* **16**, 356-365

Kubat-Silman, A.K., Dagenbach, D., Absher, J.R. (2002). Patterns of impaired verbal, spatial, and object working memory after thalamic lesions. *Brain Cogn*. **50**, 178-193

Kuwabara, H., Ohta, S., Brust, P., Meyer, E., and Gjedde, A. (1992). Density of perfused capillaries in living human brain during functional activation. Progress in Brain Research, 91, 209-15.

LaBerge, D. (1995). *Attentional Processing*. Harvard Univ. Press, Cambridge, MA

Lal, S.K.L., and Craig, A. (2001). A critical review of the psychophysiology of driver fatigue, *Biological Psychology*, Vol. 55, pp. 173-194.

Lal, S.K.L. and Craig, A (2002). Driver fatigue: Electroencephalography and psychological assessment, *Psychophysiology*, Vol. 39, pp. 313-321.

Linde, L., & Bergstorm, M. (1992) The effect of one night without sleep on problem-solving and immediate recall. *Psychol Res* **54**, 127-36

Lisper, H.O., Eriksson, B., Fagerstrom, K.O. & Lindholm, J. (1979). Diurnal variation in subsidiary reaction time in a long term driving task. Accident Analysis and Prevention, Vol 11, pp. 1-5.

MacDonald III, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* **288**, 1835-1838

Magistretti, P.J. and Pellerin, L. (1996). The contribution of astrocytes to the, 18F-2-deoxyglucose signal in PET activation studies. Molecular Psychiatry, 1, 445-52.

Magistretti, P.J., Pellerin, L., Rothman, D.L., and Shulman, R.G. (1999). Energy on demand. Science, 283, 496-7.

Makeig, S., and Inlow, M. (1993). Lapses in alertness: coherence of fluctuations in performance and EEG spectrum, *Electroencephalography and Clinical Neurophysiology*, Vol. 86, pp. 23-35.

Makeig, S & Inlow, M. (1993). Lapses in alertness: coherence of fluctuations in performance and EEG spectrum. Electroencep. clin. neurophy 86, 23-35

Mallis, M. M. (1999) Evaluation of techniques for drowsiness detection: Experiment on performance-based validation of fatigue-tracking technologies, Drexel University, June.

Matthews, P.M. (2001). An introduction to functional magnetic resonance imaging of the brain. In Functional MRI: an introduction to methods. P, Jezzaard, P.M., Matthews, S.M., Smith, ed. (New York: Oxford University Press) p 3-34

McDonald, N. (1984). Fatigue, safety and the truck driver. London: Taylor & Francis.

McCarthy, G., Blamire, A.M., Puce, A., Nobre, A.C., Bloch, G., Hyder, F., Goldmen-Rakic, P. & Shulman, R.G. (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proc Natl. Acad. Sci. USA* **91**, 8690-8694

McCarthy, M.E. & Waters, W.F. (1997). Decreased attentional responsivity during sleep deprivation: orienting response latency, amplitude and habituation. *Sleep* **20**, 115-123

Muir, D, Berl, S. and Clarke, D.D. (1986). Acetate and fluoroacetate as possible markers for glial metabolism in vivo Brain Research, 380, 336-40.

Ojeman, G.A., Fedio, P. (1968). Effect of stimulation of the human thalamus and parietal and temporal white matter on short-term memory. Journal of Neurosurgery, , Vol. 29, PP. 51-59.

Ojeman, G.A. (1981) Brain organization for language. Psychophysiology Today and Tomorrow, (Bechtereva, N.P., editor), Pergamon Press, New York, NY.

Paulesu, E., Frith, C.D., & Frackowiak, R.S.J. (1993) The neural correlates of the verbal component of working memory. *Nature* **362**, 342-345

Pauling, L. and Coryell, C. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin, and carbon monoxyhemoglobin. Prodeedings of the National Academy of Sciences (USA), 22, 210-16.

Peterson, L., Peterson, M. (1959) Short-term retention of individual verbal items. Journal of Experimental psychology, , Vol. 58, pp. 193-198.

Poitry-Yamate, C.L. and Tsacopoulos, M. (1992). Glucose metabolism in freshly isolated Muller glial cells from a mammalian retina. Journal of Comparative Neurology, 320, 257-66.

Portas, C.M., Rees, G., Howseman, A.M., Josephs, O., & Frith, C.D. (1998) A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *Jour. Neurosci.* **18**, 8979-8989

Rees, G., Friston, K. and Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5 [see comments]. Nature Neuroscience, 3, (7), 716-23.

Reichle, E.D., Carpenter, P.A. & Just, M.A. (2000) The neural bases of strategy and skill in sentence-picture verification. *Cogn. Psychol.* **40**, 261-295

Ribak, C.E. (1981). The histochemical localization of cytochrome oxidase in the dentate gyrus of the rat hippocampal. Brain Research, 212, 169-74.

Rose, L.(1969) The reading process and some research implications, Journal of reading, October,.

Rose, S.P. (1975). Cellular compartmentation of brain metabolism and its functional significance. Journal of Neuroscience Research, 1, 19-30.

Rosenbleuth, (1970). A Mind and brain. The MIT Press, Cambridge, Massachusetts. 04-607

Russell, R. (1975). Explaining the brain. Oxford University Press,

Snyder, C.D. and Wilson, J. E. (1983). Relative levels of hexokinase in isolated neuronal, astrocytic, and oligodendroglial fractions from rat brain. Journal of Neurochemistry, 40, 1178-81.

Sokoloff, L., Takahashi, S., Gotoh, J.. Driscoll, B.F.m and Law, M.J. (1996). Contribution of astroglia to functionally activated energy metabolism. Developmental Neuroscience, 18, 344-52.

Sokoloff, L. (1999). Energetics of functional activation in neural tissues. Neurochemical Research, 24, 321-29.

Stickgold, R. (1998) Sleep: off-line memory reprocessing. *Trends Cogn. Sci*. **2**, 484-492

Stickgold, R., James, L., Hobson, J.A. (2000a) Visual discrimination learning requires sleep after training. *Nature Neurosci.* **3**, 1237-1238

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V. & Hobson, J.A. (2000b) Visual discrimination task improvement: a multi-step process occurring during sleep. *J. Cogn. Sci.* **12**, 245-252

Stickgold, R., Hobson, J.A., Fosse, R., Fosse, M. (2001) Sleep, Learning, and Dreams: Off-line Memory Reprocessing. *Science* **294**, 1052-1057

Stutts, J. C., Wilkins, J. W. and Vaughn, B. V. (1999) Why Do People Have Drowsy Driving Crashes? Input from Drivers Who Just Did, Prepared for AAA Foundation for Traffic Safety.

Talairach, J., and Tournoux, P. (1988) *Co-Planar Stereotaxic Atlas of the Human Brain.* New York: Thieme.

Tepas, D.I. & Mahan, R.P. (1989). The many meanings of sleep. Work & Stress, Vol 3(1), pp. 93-102

Trooptest
(http://www.sparknotes.com/psychology/cognitive/attention/section3.rhtml#head_3_1
)

Visual search test
(http://coglab.wadsworth.com/experiments/VisualSearch/index.html)

Waard, D. De and Brookhius, K. A. (1991) Assessing driver status: A demonstration experiment on the road, *Accident Analysis and Prevention*, Vol. 23, pp.297-307,.

Williams, H.L., Granda, A.M., Jones, R.C., Lubin, A., & Armington, J.C. (1962). EEG frequency and finger pulse volume as predictors of reaction time during sleep loss. *Electroencep. clin. Neurophy.* **14**, 64-70