EFFECTS OF LIGHT AND CAFFEINE ON HUMAN SLEEPINESS AND ALERTNESS: A SIMULATED DRIVING EXPERIMENT

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STISIM Drive Simulator,

Subjective sleepiness,

Young driver

Abstract

Sleepiness remains a primary cause of road trauma, resulting in approximately 20% of the fatal crashes in Australia each year. Young adults are overrepresented in sleep-related road crashes. Sleepiness is known to lead to neurobehavioral consequences such as decreased objective or subjective alertness, and impaired cognitive and driving performance. Sleep deprivation, arising from social or occupational obligations, is a major cause of sleepiness. Young adults are particularly sensitive to the adverse effects of sleep deprivation. Drivers often rely on ineffective (e.g. opening the window, listening to music) or temporary (e.g. consumption of caffeine) countermeasures for sleepiness. Finding more effective countermeasures for driver sleepiness is of great importance. Recent description of the acute alerting effects of light has raised the possibility of light as a novel countermeasure for sleepiness. However little is known about the effects of light on sleepy drivers, especially after naturalistic partial sleep restriction.

This thesis aimed to understand the effect of blue-green light and caffeine on young drivers' sleepiness and driving performance.

Three reviews were conducted; firstly, a review of the mechanisms and models of human sleep-wake regulation, and the effects of sleep loss on a variety of human alertness and other contributors to sleepiness; secondly, a systematic review of the effects of sleep loss on young drivers' sleepiness and driving performance using GRADE criteria to formally rate quality of evidence; and finally a review of the alerting effects of bright light and caffeine on drivers' sleepiness. Based on the findings of these three reviews, a repeated-measures factorial design was adopted in an experimental study to investigate the alerting effects of light and caffeine, individually or combined together, on young drivers' alertness and performance after chronic partial sleep deprivation. Prior to the experimental study, the sleep-wake times of 30 young participants (18-25 years) were monitored via Actigraphy, and their bedtimes were reduced from 8 hours to 7 hours gradually. In the last three days of Actigraphy, participants attended three test sessions involving two 30-minute simulated drives. The first drive was conducted under dim red light (Placebo

condition) and the second under each of three randomised interventional conditions, which presented caffeinated (100 mg caffeine) or placebo non-caffeinated gum, in conjunction with either blue-green light (520 nm dominant, 230 μW/cm²) or red light (< 2 lux). Light and caffeine were provided via commercial light glasses and caffeinated chewing gums respectively.

Findings of the experimental study revealed that provision of all three interventional conditions decreased subjective sleepiness scores from "some signs of sleepiness" to "not sleepy" or even to "rather alert". However, none of these conditions improved electroencephalographic or electrocardiographic indices of alertness. Light alone did not improve drivers' psychomotor performance (reaction time indices of sleepiness), while caffeine alone and light and caffeine in combination both improved some of these indices. Each of the three conditions improved indices of driving performance, but to different extents. The absolute value of steering wheel angle found to be the most sensitive index of driving performance to sleep deprivation with a significant reduction under all three interventional conditions.

Overall, data partly supported the alerting effect of administering the intervention when compared with the placebo condition. Data were also partly in agreement with the hypothesis of a greater alerting effects of light alone, caffeine alone or the combination of them than the Placebo condition. Additionally, data partly supported the hypothesis of a greater alerting effect of light and caffeine in combination than either light alone or caffeine alone, but did not support an advantage of light alone.

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List of Abbreviations

ECG: Electrocardiography

EEG: Electroencephalography

LED: light emitting diode

NREM: None rapid eye movement

REM: Rapid eye movement

SWA: Slow wave activity

SWS: Slow wave sleep

List of Publications

Shekari Soleimanloo S, Smith S, White M, Garcia Hansen V & Leong M (2015) The effects of light on cognitive performance of partially sleep-deprived young drivers. Sleep and Biological Rhythms 13 (S1) 134:46

Shekari Soleimanloo, S., Smith, S. S., White, M. J., Garcia-Hansen, V (2015) Comparison of the effects of light and caffeine on young drivers' subjective sleepiness after chronic partial sleep deprivation.12th Australasian Injury Prevention and Safety Promotion Conference, 25-27 November 2015, Sydney, Australia

Statement of Original Authorship

The work contained in this thesis has not been previously submitted to meet requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made.

QUT Verified Signature

Signature:

Date: 19/05/2016

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Thesis Outline

This thesis has been divided in to 8 chapters as follows:

Chapter 1: Introduction

Chapter 2: Review of Effects of Sleep Loss on Drivers' Alertness and Performance

Chapter 3: A Systematic Review and the GRADE Rating Analyses of the Evidence on the Effects of Sleep Loss on Young Drivers' Performance

Chapter 4: Review of Alerting Effects of the Light and Caffeine

Chapter 5: Experimental Study

Chapter 6: The Results of the Experimental Study

Chapter 7: Discussion

Chapter 8: Conclusion

Chapter 1: Introduction

This chapter outlines the background (Section 1.1), context of the research (section 1.2), and its purposes (Section 1.3). Finally, Section 1.4 describes the significance and scope of this research.

1.1 BACKGROUND

Driving is a complex task requiring optimal cognitive, perceptual, motor and decision making skills (Campagne, Pebayle, & Muzet, 2004). While receiving multiple stimuli simultaneously from the road scene (complex visual, auditory and tactile information), the driver needs to select and analyse stimuli, and to react rapidly based on the road situation, driving regulations, conditions of the vehicle, and on their previous driving experiences (Jackson, Croft, Kennedy, Owens, & Howard, 2013). Functional magnetic resonance imaging (FMRI) has shown that different parts of human brain are involved in the driving task including the occipital, parietal, and cerebellar cortices (Spiers & Maguire, 2007). Figure 1.1 shows five human brain areas. The brain areas involved in different driving-related tasks (Spiers & Maguire, 2007) are presented in Table 1.1.

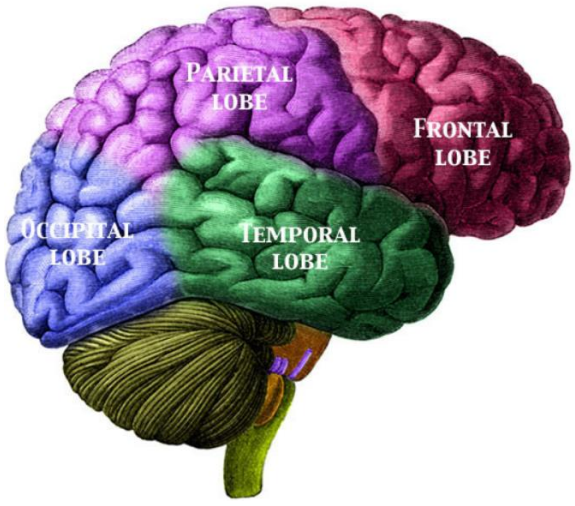

Figure 1.1 Human brain areas, (adopted from Camazine, 2008)

Table 1.1: Different brain areas activated during specific driving tasks (Spiers & Maguire, 2007)

Action while driving	Involved regions	General function	Related driving task
Performing prepared actions	parietal and cerebellar regions, pre-*SMA/SMA	prepared movement execution	starting to move mostly by the left lateral motor/premotor, turning corners, reversing and stopping, attention to visual motion,
	cerebellum	fine-control during movement execution	prepared manoeuvres with the vehicle
	medial and lateral occipital regions	all the prepared actions	visual change during all prepared actions, attention to visual motion and fixed landmarks
Responding to driving hazards	pre-SMA	action planning	choosing actions or making decisions for future actions
	parietal cortex		future intentions, planning actions
	lateral occipital cortex	visual processing	focusing on locations
	posterior parietal cortex, pre-cuneus and lateral occipital cortex	visual and attentive tracking moving objects	monitoring traffic,
Road traffic rules	the right lateral **PFC and medial PFC	rule retrieval and maintenance	spontaneous processing of rules

*Supplementary Motor Area, **Pre Frontal Cortex

Sleepiness is known to decrease brain activity and function primarily in the alertness and attention related areas such as the thalamus, the prefrontal cortex, and the posterior parietal cortices (Thomas et al., 2000), and to result in decreased cognitive performance, impaired concentration and perception, vision disturbances, slower reactions, more frequent 'micro sleep' episodes (Jackson et al., 2013; Martella, Casagrande, & Lupiáñez, 2011; Orzeł-Gryglewska, 2010), and other functions subserved by these distinct brain regions.

Estimates of the prevalence of sleepy driving vary widely between countries (i.e. in Norway 10%, in Ontario, Canada 14.5%, and in the United States 32%), possibly due to geographical or cultural differences, and/or reflecting differences in the measurement and reporting of sleepiness (Phillips & Sagberg, 2013). Sleep-related crashes represent up to 20% of all crashes in developed countries (Connor et al., 2002; Horne, J.A & Reyner, 1995; Sagaspe, P et al., 2010; Sagberg, 1999; Smolensky, Di Milia, Ohayon, & Philip, 2011; Vanlaar, Simpson, Mayhew, & Robertson, 2008). In spite of differences in the nature and quality of the studies reporting sleep-related crashes, a consensus has emerged that sleepiness is a particularly significant risk factor for severe and fatal crashes (Abe, Komada, Nishida, Hayashida, & Inoue, 2010; Horne, J.A & Reyner, 1995; McCartt, Ribner, Pack, & Hammer, 1996; Stutts, Wilkins, Osberg, & Vaughn, 2003). According to the report of the Parliament of the Commonwealth of Australia, driver sleepiness accounted for 6% of all crashes, 15% of fatal crashes, and 30% of fatal crashes on rural roads in 2000 (Papadelis et al., 2007).

Road crashes caused by sleepy driving, or other reasons, impose a very large human and financial burden on society. In Australia, estimations by the Bureau of Infrastructure Transport and Regional Economics (Bureau of Infrastructure Transport and Regional Economics [BITRE], 2009), revealed a $17.85 billion (2006 dollars) social cost of road crashes, approximately $2.4 million per fatality for human losses, approximately $214,000 per injury (including disability-related costs) for a hospitalized injury, and $2200 per injury for non-hospitalized injury in 2006. Efforts to reduce road crashes could result in decreased social, economic, and health system burdens.

1.2 CONTEXT

Young drivers (those aged between 18 and 24 years) appear to be at higher overall risk for road crashes (Campagne et al., 2004; Horne, J.A & Reyner, 1995). In some studies the risk of being involved in a traffic crash among drivers younger than 24 years has been estimated between 2 to 10 fold compared to other age groups (Åkerstedt, Kecklund, & Hörte, 2001; Sagaspe, P et al., 2010). During the last 10 years in Australia, 17–25 year-olds comprised only 13% of the population, but had the highest rate (22%) of road-related fatalities (Bureau of Infrastructure Transport and Regional Economics (BITRE), 2013). Consistent with this figure, in 2012 more than 140 drivers out of 600 fatalities of drivers in Australian roads were in the 17–25 age group (Bureau of Infrastructure Transport and Regional Economics (BITRE), 2013).

It remains possible that sleepiness-related crashes are even more common than generally reflected in these statistics. This may be due to the lack of an objective test for measuring sleepiness, and confusion or misattribution regarding the constructs of fatigue, inattention, and sleepiness. This confusion has been driven by a lack of specificity around these constructs, and interchangeable use of these terms in the literature. Sleepiness can be defined as a person's inability to maintain wakefulness and their tendency to doze off or to fall asleep (Cluydts, De Valck, Verstraeten, & Theys, 2002). Fatigue can be considered as a gradual process of disinclination towards effort which may not be directly observable or measured, but eventually impairs performance on a range of cognitive and psychomotor tasks (Lal & Craig, 2001$_{(b);}$ Philip et al., 2005$_{(a);}$ Williamson, A. et al., 2011), including tasks critical for safe driving.

The higher risk of being involved in a crash among young drivers is partly due to a range of cohort-related factors, including being inexperienced in driving, increased social deviance and broader risk involvement (including increased use of alcohol and other drugs), peer influence, and even car preference (Smith, S., Horswill, Chambers, & Wetton, 2009$_{(b)}$). However, even in that context, sleepiness remains a very substantial primary contributor to crashes (Åkerstedt et al., 2001; Cummings, Koepsell, MoVat, & Rivara, 2001; Lowden, Anund, Kecklund, Peters, & Åkerstedt, 2009). There are a number of contributors to increased sleepiness among young

drivers including social factors (socialization and work patterns), disrupted sleep patterns, and driving when ordinarily asleep (particularly late at night and in the early morning (Smith, S. et al., 2009$_{(b)}$). Some of the behaviours that lead to increased sleepiness interact with sleepiness as risk factors, and may be amplified by sleepiness, are subserved by neurophysiological processes specific to the late adolescent and young adult cohort. One such process is the maturation of the dorsolateral prefrontal cortex (DLPFC), a functional region associated with proper judgment and decision-making (Beeli, Koeneke, Gasser, & Jancke, 2008).

While acute sleep deprivation has been shown to impact on driving skills, the effects of more naturalistic chronic sleep deprivation (i.e. long term partial sleep restriction or partial sleep disruption typical in this age cohort) is less well described. This naturalistic element may be important for linking laboratory research to the on-road, epidemiological, and crash-data based studies.

There are two obvious solutions to sleepy driving; the first and the best solution for sleepiness is to control circadian rhythmicity and to not drive when sleepy (MacLean, Davies, & Thiele, 2003). However, drivers may often not be able to achieve sufficient sleep, may in any case underestimate their sleepiness, and may prefer to adopt countermeasures when sleepy due to commercial and social pressures (Anund, Kecklund, Peters, & ÅKerstedt, 2008$_{(a);}$ Horne, J.A & Reyner, 1996; Reyner, L. & Horne, 1998; Rogers, P.J et al., 2005$_{(b);}$ Van Dongen, Maislin, Mullington, & Dinges, 2003).

The second solution is not to be sleepy when driving; one contemporary countermeasure for sleepiness is taking a nap. In one study, a nap was perceived as an effective countermeasure for sleepiness by 70% of drivers (Nordbakke & Sagberg, 2007). However, there are some flaws in taking the nap after sleep loss. A study among shift worker participants reported poor daytime sleep quality due to difficulty in falling asleep, sleep latency of about 20 minutes and early awakening after falling asleep (Garbarino, Nobili, Beelke, & Balestra, 2002). One important drawback of the nap is sleep inertia (a biological tendency to feel not fully awake) after the nap. For example in a 40-min simulated driving experiment in the early morning after one night sleep loss the objective evidence of sleep inertia was observed immediately after a 10-min nap as deteriorated PVT performance (Hilditch,

Dorrian, Centofanti, Van Dongen, & Banks, 2015). This means that drivers are not fully alert immediately after taking the nap, and for some time thereafter. Additionally, the existing regulation of maximum driving time only applies to professional drivers and there is no obligatory regulation for non-professional drivers to stop and take a nap (MacLean et al., 2003).

Caffeine, another commonly used countermeasure, is cheap and readily accessible, has few harmful side effects and is socially acceptable. Caffeine has a very rapid oral absorption (Blanchard & Sawers, 1983) and has been shown to restore performance to baseline levels after sleep loss (Smith, A., 2002).

Despite the potential effectiveness of caffeine, 20% of people do not habitually use caffeinated beverages (Heckman, Weil, Mejia, & Gonzalez, 2010; Mets, Baas, van Boven, Olivier, & Verster, 2012), or are genetically sensitive to caffeine (Landolt, 2012). Additionally, the alerting effects of caffeine do not typically appear until 30 minutes after consumption and last only for about one hour (Blanchard & Sawers, 1983; O'connell & Zurzola, 1984).

In Australia, some televised educational campaigns have been launched, including "Join the drive, driving tired" (Department of Transport and Main Roads, 2015), "Ride to live", "Stop revive survive", "Driver reviver" (NSW Centre for Road Safety, 2015). Additionally, in the state of New South Wales (NSW) a downloadable map of rest areas in major roads has been provided (NSW Centre for Road Safety, 2015). Nevertheless, there are no data available to show that these population-level interventions are efficacious, and the rates of sleep-related crashes remain very high despite these campaigns. There remains a need to look for other alternatives to improve the 'armoury' available to solve this problem.

Recently, the possible alerting effects of light have received increasing attention (Cajochen, C., 2007; Kaida, Takahashi, & Haratani, $2006_{(b)}$). Light can affect brain function and cognition by activating alertness-related pathways in subcortical structures and mood-related pathways in the limbic areas, followed by modulation of cortical area activities (Chellappa et al., 2011; Smolders, de Kort, & Cluitmans, 2012; Vandewalle, Maquet, & Dijk, 2009). Light directly elicits instantaneous changes in physiological arousal (Smolders et al., 2012; Stephenson, Schroder, Bertschy, & Bourgin, 2012; Thessing, Anch, Muehlbach, Schweitzer, & Walsh,

1994), improvement of both subjective and objective alertness at night and during the day (Figueiro, M.G, Bullough, & Rea, 2007a; Horowitz, Cade, Wolfe, & Czeisler, 2001; Lockley et al., 2006; Revell, Arendt, Fogg, & Skene, 2006; Rüger, Gordijn, Beersma, De Vries, & Daan, 2006), reduction of sleepiness (Figueiro, M.G et al., 2007a; Horowitz et al., 2001; Rüger et al., 2006; Vandewalle et al., 2009), improvement of mood (Rüger et al., 2006; Stephenson et al., 2012), enhancement of cognitive performance (Rüger et al., 2006; Stephenson et al., 2012; Thessing et al., 1994), particularly psychomotor vigilance reaction times (Lockley et al., 2006), reduction of attention failures (as measured by EOG slow rolling eye movements), and suppression of EEG alpha-theta ($\alpha+\theta$; 5-9 Hz) activity, regarded as markers of sleepiness in the waking electroencephalogram (Lockley et al., 2006). While all these studies strongly suggest that light acts as an alerting agent when sleepy, they do not clearly show that the light has alerting effects on drivers who are *chronically* sleep restricted. These studies do not demonstrate that light is efficacious for all driving-related tasks (Table 4.2).

Acute sleep deprivation remains the dominant experimental manipulation of sleep, but it is becoming clear that the effects (on metabolism, cognition and safety) of chronic sleep deprivation might differ from those exposed by acute deprivation. This has been demonstrated in both animal and human models. It is expected that performance after chronic sleep deprivation may differ from after acute deprivation, but may better reflect the 'real world' experience of young adults (Novati, Hulshof, Granic, & Meerlo, 2012; Philip et al., 2012). Taking the limitations of existing studies of sleepy driving in the vulnerable young adult population into account, there is a critical need to assess the potential of light as a novel countermeasure for sleepiness in this context, either alone or combined with existing strategies such as caffeine.

1.3 PURPOSE OF THIS RESEARCH

In general, this program of research aimed to investigate the nature and magnitude of any alerting effect of light among young drivers when sleepy. A number of light delivery systems have now been commercialized and are widely available. These devices are primarily marketed as therapies for circadian rhythm disorders or for

seasonal affective disorders. Similarly, new modes of caffeine delivery (specifically caffeinated gums) are now widely available, and promoted as alerting agents. An overarching pragmatic aim of this research program was to determine the potential benefit of these types of contemporary interventions for driver safety when sleepy. To address this aim, the program of research was developed as a four-part research protocol.

Firstly, in order to address the consequences of sleep loss, a primary literature review was performed to understand the concepts of sleepiness and alertness and the relationship between them, mechanisms of sleepiness, models of sleep-wake regulations, the contributors to sleepiness and the adverse effects of sleep deprivation on drivers of all levels including objective sleepiness, subjective sleepiness and driving performance.

Secondly, a systematic review was conducted to explore the specific effects of *chronic sleep loss* on young drivers' *daytime driving performance* and to evaluate the quality of the available body of evidence.

Thirdly, a literature review of the alerting effects of light and caffeine on driver's sleepiness was undertaken. This review highlighted some known and unknown facts about the alerting effects of light and caffeine which were of importance to the main study (experimental study).

Finally, an experimental study was undertaken to determine the alerting effects of a standardized 'dose' of light and caffeine when administered alone or in combination on young drivers' daytime sleepiness after chronic partial sleep loss. For this purpose six primary research questions were posed (Table 1.2). Six specific hypotheses were also developed to address each of these research questions as shown in Table 1.3.

Table 1.2: Research questions

Research Question	Description
Research Q1	Does light have any alerting effect on drivers' objective, subjective, cognitive performance or driving performance measures of sleepiness after chronic partial sleep loss?
Research Q2	Do low levels of caffeine light have any alerting effect on drivers' objective, subjective, cognitive performance or driving performance measures of sleepiness after chronic partial sleep loss?
Research Q3	Does the combination of light and caffeine have any alerting effect on drivers' objective, subjective, cognitive performance or driving performance measures of sleepiness after chronic partial sleep loss?
Research Q4	Are there any significant differences between alerting effects of the combination of light and caffeine on objective, subjective, cognitive performance and driving performance measures of sleepiness as compared to those of light or caffeine?
Research Q5	Is there any significant difference between alerting effects of light on objective, subjective, cognitive performance and driving performance measures of sleepiness as compared to those of caffeine?
Research Q6	Is there any significant overall difference between objective, subjective, cognitive performance and driving performance measures of sleepiness after intervention when compared with the Placebo condition?

Table 1.3: Research hypotheses to answer the research questions

Hypothesis	Description
Hypothesis 1	Light (condition 2) has an alerting effect relative to the Placebo condition (condition 4)
Hypothesis 2	Caffeine (condition 3) has an alerting effect compared to the Placebo condition (condition 4)
Hypothesis 3	Light and caffeine in combination (condition 1) has an alerting effect compared to the Placebo condition (condition 4)
Hypothesis 4	Light and caffeine in combination (condition 1) has a greater alerting effect than either light or caffeine alone
Hypothesis 5	Light alone has a greater alerting effect than caffeine alone
Hypothesis 6	Administration of any intervention has an alerting effect compared to the Placebo condition

1.4 SIGNIFICANCE, SCOPE AND DEFINITIONS

This program of research was intended to contribute to new knowledge by addressing some key methodological limitations identified in existing research (including aspects of study design, sample characteristics, the quality and quantity of intervention, and control for confounders). All four components of this research are of importance. The first part, review of effects of sleep loss on drivers' alertness and performance, identified the most sensitive outcome measures associated with sleepiness in all levels including objective and subjective sleepiness and driving performance. The second part, a systematic review of the effects of sleep loss on young drivers' performance, highlighted the driving performance outcomes most sensitive to chronic sleep loss in young drivers during the daytime, and identified the existing gaps in this knowledge. The third part, review of the alerting effect of light and caffeine, addressed current knowledge on the alerting effects of bright light and caffeine in the driving context, particularly light and caffeine in combination. The outcomes of these three reviews informed the framework of the fourth part, the experimental study in terms of inclusion and exclusion criteria, the size and characteristics of the sample, study design, the doses and timing of administration of the light and caffeine, and the outcome measures of sleepiness. As a result, the experimental study included a number of specific aspects as follows:

The design of the experimental study was a repeated-measures, within-subjects design. The repeated-measures facet of this study enabled the researchers to examine cumulative effects of sleep loss over a period of three days, while the within-subjects aspect eliminated most of inter-individual differences such as age, gender, driving experience, and individual sensitivity to sleep loss. The sample in the experimental study comprised 30 young non-professional and non-shift-worker drivers aged 18-25 years. This age group represented the most vulnerable drivers to sleep loss (Smith, M. R., Fogg, & Eastman, $2009_{(a)}$), and the most involved drivers in sleepiness-related crashes. Regarding the quality of sleep loss as an intervention, gradual bedtime restriction was induced to examine the effects of chronic sleep loss over a week. The severity of total sleep loss was quite low, a one-hour reduction of time in bed, to examine the effects of naturalistic levels of sleep loss. This study revealed some new

findings about the relative alerting effects of light and caffeine in the daytime after chronic mild sleep loss among young drivers.

Chapter 2: Review of Effects of Sleep Loss on Drivers' Alertness and Performance

This chapter provides a review of the literature on the following topics: mechanisms and models of human sleep/wake regulation (Section 2.1), alertness (Section 2.2), characteristics of human arousal (Section 2.3), the adverse effects of sleep deprivation (Section 2.4), and other contributors to sleepiness (Section 2.5). Section 2.6 provides a summary of the literature reviewed and explains the corresponding implications for the current research program.

2.1 MECHANISMS AND MODELS OF HUMAN SLEEP/WAKE REGULATION

Sleep is a state driven by a biological rhythm that is synchronized to the solar day, and responds to a need for recovery or recuperation (Beersma, D. G. M., 1998; Borbély, 1982). Sleep can be characterized by its period (length of rhythm), phase (timing of rhythm), and amplitude (magnitude of rhythm). The alternation between sleep and wake is driven by a very complex neurobiology (Van Dongen & Dinges, 2005). Two primary factors appear to be vital for modulating sleepiness and alertness at any point of time; the *homeostatic* and *circadian* drives that interact but originate from distinct brain mechanisms and neurotransmitter systems.

The circadian process is mediated by circadian pacemakers in the suprachiasmatic nucleus (SCN) of the anterior hypo-thalamus (Cluydts et al., 2002; Moore, 2006). The circadian pacemaker is actually a web of oscillator neurons which receives light-dark information from the inner retina of the eye via photoreceptor peptides, melanopsin (Moore, 2006). Melanopsin contributes to the light response of intrinsically photosensitive retinal ganglion cells (ipRGCs) in the retina (Zele, Feigl, Smith, & Markwell, 2011). The ipRGCs are maximally sensitive to the 'blue' range of visible light, that is, light with wavelength around 460-480 nm (Appleman,

Figueiro, & Rea, 2013; Gooley et al., 2010; Lockley et al., 2006; Münch, Linhart, Borisuit, Jaeggi, & Scartezzini, 2012; Postolache & Oren, 2005; Revell et al., 2006; Stephenson et al., 2012; Zele et al., 2011). Light passes through the ganglion cell layer before reaching the rods (R) and cones (C), and elicits an intrinsic response in the IpRGCs (Figure 2.1). Additional light (indirect input) information is transferred from rods and cones to the ganglion cells (G) via the second-order bipolar cells (B) and complements the initial intrinsic response of IpRGCs (Vandewalle et al., 2009). That is, while the IpRGC's are non-image-forming cells, they also transduce light information from the rods and cones (Gronfier, 2013).

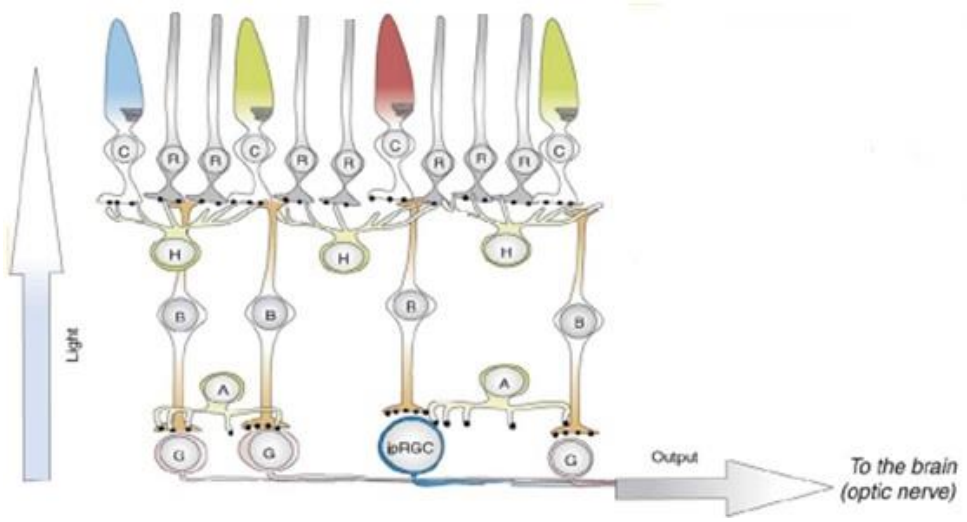

Figure 2.1. Mechanism of non-visual effects of light including circadian rhythm of sleep-wake regulation, 'A' depicts retinal cells (adopted from Vandewalle et al., 2009).

Light information is transferred to the brain via the optic nerve and directly or indirectly innervates a range of neural sites associated with sleep-wake regulation including hypothalamic nuclei such as the supreachiasmatic nuclei (SCN; including the central circadian pacemaker), the ventro-lateral preoptic nucleus (VLPO), which contains sleep active neurons, the lateral hypothalamic area (LH) which regulates wakefulness, the olivary pretectal nuclei (OPN) involved in pupillary constriction

(and therefore the pupillary light response), the amygdala (MA) involved in emotion regulation, as well as areas typically involved in vision such as the thalamic lateral geniculate nuclei (LGv/d), and the brainstem superior colliculus (SC) (Vandewalle et al., 2009). The brain regions implicated in light pathways are exhibited in Figure 2.2.

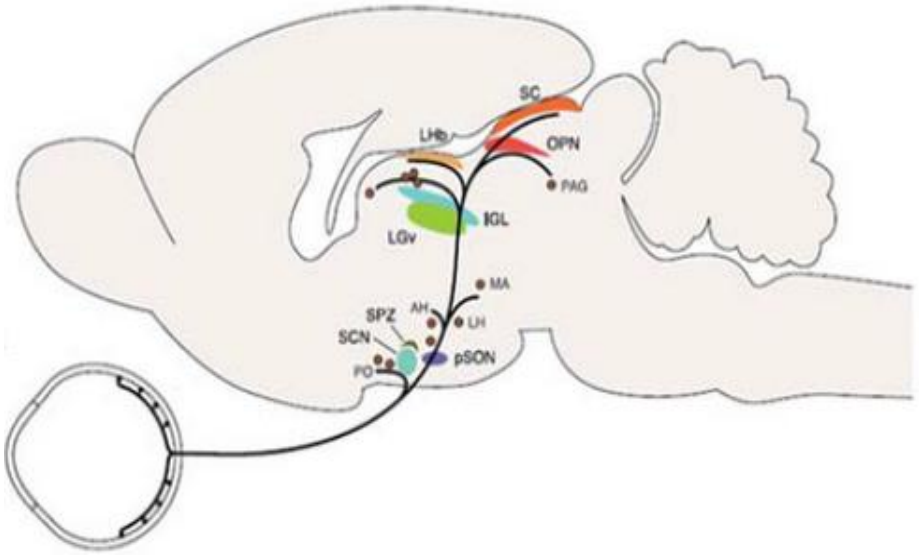

Figure 2.2. Non-visual pathways of light in the brain of male Sprague Dawley rats in cross section, (adopted from Gronfier, 2013). The sagittal section, the bulb at the front is the eyeball.

The homeostatic process however, is neither primarily modulated by time of day, nor by a single locus in the CNS, but reflects a cumulative process that increases with wake time, and involves several distinct but interacting neural systems such as monoamine, neuropeptide, and cytokine transmitters in the hypothalamus, basal forebrain, and brain stem nuclei (Toppila & Porkka-Heiskanen, 1999). As an example, in the basal forebrain, homeostatic processes are mediated by a progressive increase in adenosine levels after prolonged wakefulness, and by slow decrease during recovery sleep (Cluydts et al., 2002; Porkka-Heiskanen et al., 1997).

A number of sleep regulation models have been developed to summarise observations of sleep processes. These models do not generally concentrate on sleepiness, but more on the dynamics of sleep-wake regulation. The basic

quantitative model of human sleep regulation, known as the 'two-process' model of sleep regulation, was proposed by Borbély (1982). Other models have also been developed by adding to or refining the two-process model, including the ultradian model, the three-process model of alertness regulation (Folkard & Åkerstedt, 1987), the two opponent-process model (Edgar, Dement, & Fuller, 1993), and the four-process model of sleep-wake (Johns, Murray, 1998). These models each describe the basis of sleepiness and alertness in different ways, and are discussed in more detail as follows.

2.1.1 **The two-process model of human sleep regulation**

Two-process model delineates the processes involved in sleep-wake and stipulates that the timing of the alternation between human sleep and wake is regulated by an interaction between a circadian process and a homeostatic process (Bonnet, M.H & Arand, 1999; Cluydts et al., 2002).

The term circadian refers to a near-24-hour cycle (Van Dongen & Dinges, 2005). The circadian process, in this group of models termed process C, is basically a clock-like mechanism and is conceived as largely independent of prior sleep and wake. The relative phase position and skewed sine-wave shape of the circadian process in this model was initially derived from sleep duration data obtained at different times of day and night (Borbély & Achermann, 1992). The circadian process regulates the appropriate timing of sleep (Toppila & Porkka-Heiskanen, 1999), and seeks to constrain adult human wakefulness to the daytime hours, and sleep during the night time hours (Van Dongen & Dinges, 2005). The daily variations in the circadian process are exhibited in Figure 2.3 (left panel).

The homeostatic process, also known as process S, refers to a build-up of homeostatic pressure (sleep propensity) for sleep during periods of wakefulness (Philip et al., $2005_{(a);}$ Van Dongen & Dinges, 2005). The model suggests that the homeostatic pressure to sleep rises in a monotonically saturating way during wakefulness, over a period of about 18 hours, and then declines exponentially during subsequent sleep (Beersma, D. G., Daan, & Dijk, 1987; Borbély, 1982). Process S depends on the amount of prior wake and/or prior sleep, and accounts for the 'sufficiency' of sleep (Toppila & Porkka-Heiskanen, 1999). As prior wake time

increases, and prior sleep time decreases, process S strengthens (Cluydts et al., 2002). In addition to regulation of the time spent awake and asleep, this process acts to consolidate sleep towards the end of the sleep episode, and influences the distribution of sleep stages within the sleep episode (Duffy, Zeitzer, & Czeisler, 2007). The time-course of the homeostatic process has been principally derived from power in slow-wave EEG frequencies delta (Achermann & Borbély, 1998; Borb & Achermann, 1999), and theta activity (Borbély & Achermann, 1992; Ferrara & De Gennaro, 2011). Based on the initial and final levels of process S during both normal sleep and recovery sleep after sleep loss, this model also suggests that during a daytime nap the homeostatic process decreases, hence slow wave activity declines in subsequent night time sleep (Borbély & Achermann, 1992). Figure 2.3 (left panel) shows the daily variations in the homeostatic process.

The two-process model assumes that the timing of sleep-wake cycle is determined by an interaction between the homeostatic process and circadian process, such that the intersection of these two processes results in sleep or wake onset (Natesan, Cho, & Koshida, 2006), and non-linear variations in sleepiness across the day (Philip et al., $2005_{(a)}$). The net effect of this interaction is a sustained period of wakefulness during the day. At night before falling asleep, circadian pressure for wakefulness gradually withdraws, whereas the homeostatic pressure for sleep continues to accumulate. Consequently, there is an increase in sleep propensity, and sleep is more likely to occur (Van Dongen & Dinges, 2005). Figure 2.3 (right panel) demonstrates the interaction of two processes S & C.

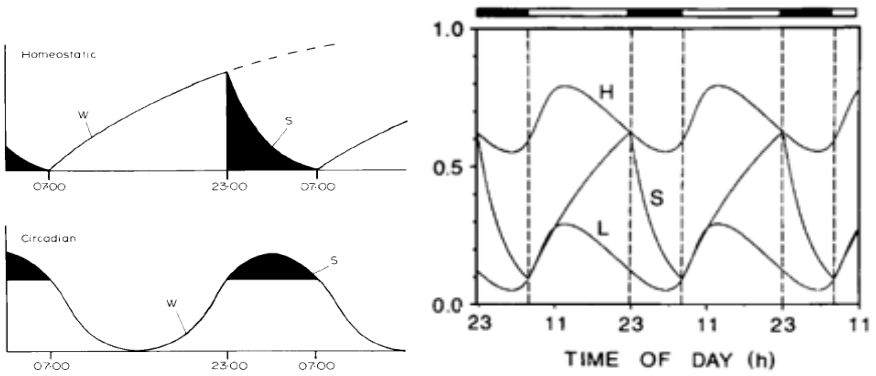

Figure 2.3. The homeostatic and circadian processes of sleep and their interaction; Left panel shows homeostatic and circadian processes during wake (W) and sleep (S), (adopted from Borbély & Achermann, 1992). Right panel shows the interaction of two processes. Process S rises during waking (white bars) and declines during sleep (black bars), (adopted from Achermann & Borbély, 1990).

A variety of experiments have been undertaken to test the assumptions of the two-process model. For instance, Åkerstedt (1986) confirmed the independency of homeostatic and circadian processes, as was assumed in the original model, by utilizing bright light to shift the circadian phase of process C without changing the time course of process S (determined by Slow Wave Activity, SWA). The saturating function describing the increase in homeostatic pressure during wake time has also been confirmed by examining the time course of SWA during daytime naps after different waking times (Beersma, D. G. et al., 1987; Dijk, Beersma, & Daan, 1987) or during long sleep periods (Dijk, Brunner, & Borbély, 1990b). The decrease of SWA during sleep after daytime naps has been confirmed by Feinberg, et al.(1985), Daan, et al. (1988) and Knowles, et al. (1990) The observations of an increased SWA during daytime naps following one night partial sleep loss (Åkerstedt & Gillberg, 1986; Gillberg & Åkerstedt, 1991) supports the assumption of the model that shortening sleep strengthens the SWA during subsequent sleep periods.

Although the two process model has been most often adopted to predict the effects of acute sleep loss, it has also been used to predict SWA after chronic sleep loss. Brunner et al. (1990) reported that two nights of sleep restricted to the first 4 hours of the habitual bedtime period (without decreasing SWA) only induced a minor increase

in SWA during recovery sleep. The two-process model accurately predicted these findings.

2.1.2 **The ultradian process during sleep**

An ultradian rhythm of sleep (that is, cyclic rhythms within the NREM-REM cycle) was initially recognized by Dement and Kleitman (1957). However, Achermann (1990; 1993) elaborated the two-process model and included the regulation of NREM and REM sleep by "ultradian process". Using this model, it is possible to predict the time course of SWA during normal sleep, and after manipulations of sleep such as partial sleep loss, after selective slow wave sleep loss, after a daytime nap, during prolonged sleep period, or during prolonged wakefulness (Achermann & Borbély, 1990; Borb & Achermann, 1999; Borbély & Achermann, 1992). Furthermore, the interaction of circadian and homeostatic processes in this model could predict timing of sleep-wake transitions as well as timing of daytime alertness (Borb & Achermann, 1999).

Based on predictions from the ultradian model some researchers sought to examine the effect of selective sleep loss on human daytime performance. Findings of forced desynchrony (FD) protocols showed that no manipulations of Stage 1, Stage 2, or SWA sleep could elicit impairment in human cognitive performance when measured by a 5-min serial addition and subtraction (SAS) task and a digit symbol substitution (DSS) task. In contrast, specific reductions in REM sleep duration were associated with a poorer waking performance (Darwent et al., 2010). These findings imply that cognitive performance may be more sensitive to a reduction, disruption or restriction of REM sleep (a sleep architecture state more likely to occur later in the sleep episode) than from disruption of NREM/SWS sleep. The ultradian model identifies the importance of the *type* of sleep loss in manipulation of sleep. This has direct implications for the methodologies used in studies that restrict sleep. For example, sleep loss exerted by awakening participants earlier in the morning might impact on REM sleep duration, in contrast to extension of wake (staying up later) that might predominantly impact on NREM sleep duration.

2.1.3 **The three-process model of alertness**

This model was first introduced by Folkard & Åkerstedt (1987) to predict variations in alertness due to irregular sleep/wake patterns (Åkerstedt & Folkard, 1997). A third factor (process W) was added to the other two components (circadian and homeostatic processes) of the original two-process model (Figure 2.4). This additional process is known as *sleep inertia*, which is observed as a drop in alertness experienced immediately after awakening, and for up to a few hours thereafter (Åkerstedt & Folkard, 1995$_{(b);}$ Cluydts et al., 2002). In this model S + C represents the predicted alertness during 24 hours wakefulness (i.e. one night total sleep loss). This condition induces a decline of alertness during the night, with a trough in the early morning.

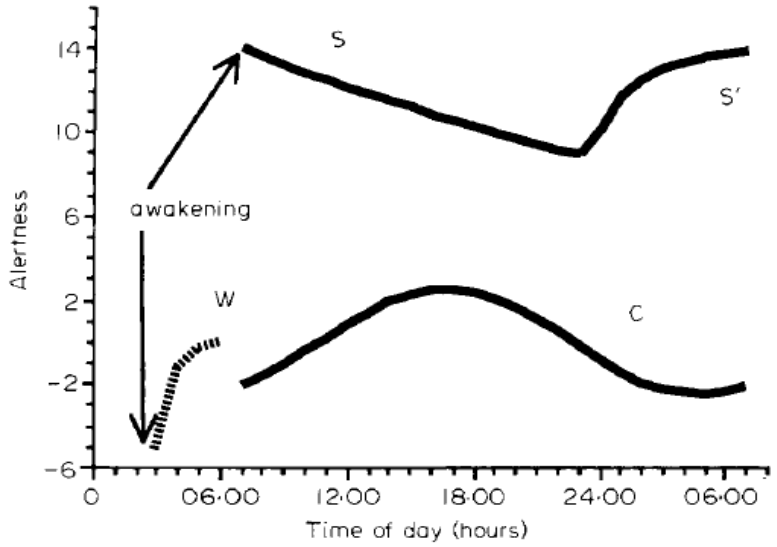

Figure 2.4. Parameters of the three-process model of alertness regulation; C = circadian component; S = homeostatic component; W = sleep inertia component (adopted from Åkerstedt, Gillberg, & Folkard, 1992).

The outputs of this model, measured by changes in objective and subjective alertness due to altered sleep/wake patterns, have been validated against subjective sleepiness ratings (predominantly the Karolinska Sleepiness Scale, KSS), and EOG slow eye movements and alpha (α; 8-12 Hz) power density (Åkerstedt & Folkard, 1995$_{(b)}$).

Comparison of the alertness scale (levels ranging from 1 to 16) and KSS scale revealed that there is some correspondence between the predicted performance and self-rated alertness (Åkerstedt & Folkard, 1995$_{(b)}$).

However, this original model was based on circumstances of acute sleep loss (e.g. one full night without sleep), and could not predict the effects of chronic partial sleep loss (a number of nights of restricted sleep) because of the high steepness of the modelled recovery function (Åkerstedt & Folkard, 1995$_{(b)}$). In this model, at sleep onset, process S is reversed (called S′) and recovery occurs in an exponential rate such that, total recovery is usually accomplished in 8 hours. This steepness increases with increasing sleep loss, hence resulting in a rapid and unreasonable prediction of the recovery (Åkerstedt, Ingre, Kecklund, Folkard, & Axelsson, 2008).

Åkerstedt & Folkard (1996$_{(b)}$) elaborated this model by changing the exponential rise of S′ to a slower linear one, and published an alertness nomogram that describes the predicted alertness under conditions of chronic partial sleep loss. Although, this modified model exhibited a slow increase in sleepiness due to partial sleep loss and a slow decrease in sleepiness during the recovery days, it could not accurately describe the mechanisms behind the sleepiness. In this model a transitional state of lowered alertness upon awaking from sleep, termed process W, was introduced. Process W is related to the circadian and homeostatic processes and has been found to induce a detrimental effect on cognition up to 4 h after awakening depending on prior sleep duration (Cajochen, C., 2007). The three-process model has been also used to predict group means for duration of sleep (Åkerstedt & Folkard, 1996$_{(a)}$) and to predict sleep latency associated with irregular sleep/wake patterns (Åkerstedt & Folkard, 1996$_{(b)}$).

The two and the three-process models of sleepiness-alertness share some common shortcomings: firstly, these models of sleep propensity are based on data drawn from studies of acute total sleep loss (Åkerstedt et al., 2008), hence there is not much evidence to support these models for prediction of the effects of accumulated sleepiness due to chronic partial sleep loss (Van Dongen, 2004$_{(a)}$). Secondly, the contribution of factors other than the model parameters to sleepiness is obvious. These include the influence of ultradian rhythms, which provoke afternoon sleepiness (Cluydts et al., 2002), environmental factors (including light), stress, sleep disorders, drugs (including both stimulants and sedatives), and general health status

(Åkerstedt & Folkard, 1995$_{(b)}$). Thirdly, these models have been validated against group data, and generally are not able to predict individual-level effects (Åkerstedt & Folkard, 1995$_{(b)}$; Cluydts et al., 2002). Fourthly, although in these models the effect of contributing factors of sleepiness, processes S and C, seems plausible, the relative importance of each factor is not clear. In other words, the primary factor with the most decisive role has not been specified. There is some evidence that, under normal conditions, the circadian process has a more fundamental effect than does the homeostatic influence, but that the homeostatic process becomes more important in sleep-deprived conditions (Cluydts et al., 2002). Finally, these models exclusively emphasize the *drive to sleep* whereas there appears to be an important corollary role for the *drive to wake* (Cluydts et al., 2002).

2.1.4 **The two opponent processes of sleep–wake regulation**

The two opponent process of sleep-wake regulation contradicts the assumption of the independency of homeostatic and circadian drives described in the two-process model. The idea of two-opponent sleep-wake regulation was first stated by Edgar et al. (1993) when they found that disruption of the SCN in monkeys caused disruption of the circadian timing of sleep, increased duration of sleep, and decreased wake duration. These findings contradicted the prediction of the two-process model of sleep regulation about the independency of the homeostatic process and overall sleep duration from the circadian process (Schwartz & Roth, 2008).

According to the two-opponent process model of sleep regulation, sleep and wake are not a simple continuum, but are competing states. The circadian process promotes waking by controlling the timing of the sleep-wake cycle and the offset of sleep. Therefore, the circadian process opposes the homeostatic process which promotes sleep. In this model, circadian oscillations originate from SCN-dependent mechanisms and comprise part of the sleep drive. In contrast, the conventional two-process model assumes that circadian processes control sleep propensity to determine wake and sleep onsets.

2.1.5 **The four-process model of sleep and wakefulness**

Johns (1998) incorporated wake drive into the two-opponent model and named it the 'four-process model of sleep and wakefulness'. In this model Johns proposed that the *relative* strength, rather than the *absolute* strength of wake and sleep drives controls falling asleep, sleepiness, hypo-vigilance, and the physiological signs of sleepiness (Cluydts et al., 2002; Johns, Murray, 1998). Moreover, Johns emphasized the importance of sleep-inducing effects of environmental contributors to the wake drive, contributions that had been largely ignored previously (Cluydts et al., 2002). In this model, the primary components subserving the sleep and wake drives originate from different neuronal groups within the central nervous system and are defined as follows:

1. The primary wake drive corresponds to process C in the two-process model. This is an intrinsic circadian rhythm, generated in the central nervous system, which ordinarily peaks at 7 to 9 p.m. and drops at 4 to 5 am in 'normal' night sleepers. Environmental and behavioural factors can shift the phase of the circadian rhythm, and change the levels of circadian indicators such as core temperature, cortisol secretion, melatonin secretion, and REM sleep.
2. The secondary wake drive mainly originates from postural factors such as movement and position of muscles, joints, and other factors such as audio-visual inputs. This secondary wake drive can be controlled voluntarily.
3. The primary sleep drive originates from intrinsic activity in various neuronal centres promoting NREM sleep with maximum activity between 10 p.m. and midnight. This drive is associated with the secretion of thyroid stimulating hormone, and could explain the reappearance of delta-waves in the latter part of sleep or inter-individual difference in delta-wave activity.
4. The secondary sleep drive corresponds to process S (in the two-process model) with a progressive rise during wakefulness and a drop during NREM sleep.

The four-process model suggests a way to combine the disparate aspects of the three-process model and the two opponent processes model, and incorporates a role for

exogenous factors. However, this 'model' has not been explicitly tested against data, and has no computational form (i.e. it exists as a schematic only).

2.2 ALERTNESS

Alertness is part of the attention system. Posner & Petersen (1990) proposed a three-network model for the attention system. This system comprises three specialized neural networks of alerting, orienting and executive control. The alerting network refers to two components of phasic and tonic alertness. In the alerting network, phasic alertness is defined as activation of the cognitive system and increased readiness to response to an external stimulus, while tonic alertness (also known as intrinsic alertness, vigilance, or sustained attention) refers to the maintenance of activity of the cognitive system (wakefulness and arousal). In this thesis the term "alertness" refers to tonic alertness. The orienting network refers to the selection of information from numerous sensory inputs. This selective function directs attention towards a visual area or object. Finally, an executive control function is associated with more complex mental activities while detecting and resolving conflicts between computations in the brain (Fan et al., 2009; Martella et al., 2011; Posner, Michael I & Fan, 2004; Posner, Michael I. & Petersen, 1990).

Alertness and sleepiness are strongly correlated with each other so that different aspects of attention have been measured by some correlates of sleepiness including 1) different subjective sleepiness scales; 2) physiologic correlates of sleepiness (e.g., electroencephalogram EEG, sleep latencies, pupillometric parameters); and 3) cognitive performance tests (Kraemer et al., 2000). Despite this physiological and functional interplay between mechanisms of sleep-wake and those of alertness, sleepiness and alertness are not reciprocal constructs (Moller, Devins, Shen, & Shapiro, 2006). There is not a straightforward slope from one to the other instead there is a lurch in the variation of alertness. The time-of-day variation in tonic alertness has a close relationship with the circadian rhythm as observed in core body temperature. The circadian rhythm of alertness is a normal physiological phenomenon, but it may have a synergistic effect on sleepiness during certain times of day (Vakulin et al., 2007; Vandewalle et al., 2009; Weeb et al., 1998). Figure 2.5 shows the time-of-day alterations of sleepiness and alertness. The alertness level is

typically highest at two times of the day - around 10 a.m. and 9 p.m. There are two main periods of decreased alertness; in the early morning at the minimum core body temperature (the temperature nadir) when circadian drive for sleep is greatest (Cluydts et al., 2002), usually between 1 and 6 a.m. (Campagne et al., 2004; Lenné, M. G, Triggs, & et al., 1997; Lowden et al., 2009; Otmani, Pebayle, Roge, & Muzet, 2005; Reimer, D'Ambrosio, & Coughlin, 2007), and again between 1 and 4 p.m. (Campagne et al., 2004; Lenné, M. G et al., 1997; Otmani et al., 2005) because of increased circadian sleep propensity in the afternoon (known as the 'post-lunch dip').

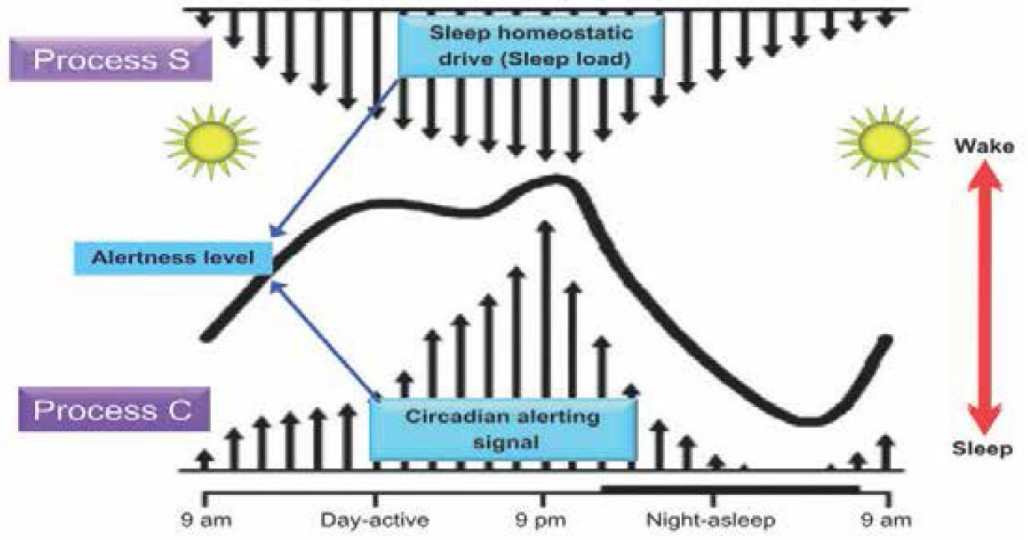

Figure 2.5. Circadian rhythm of sleepiness and alertness (adopted from Shahali & Amirabadi Farahani, 2013).

Apart from the circadian rhythm of alertness, sleep deprivation causes instability in alertness. Of all the components of the attention system, tonic alertness (vigilance) is the component most sensitive to sleep deprivation (Lim & Dinges, 2008). Acute total sleep loss could reduce brain activity, particularly in the cortico-thalamic networks involved in cognitive performance and alertness (Thomas et al., 2000). Extended wake times of more than 16 hours (providing high homeostatic sleep pressure), and sleep inertia (i.e. upon awaking from sleep) also impair human alertness (Cajochen,

C., 2007). Chronic partial sleep deprivation leads to cumulative performance deficits similar to those observed after total sleep deprivation (Van Dongen & Dinges, 2005).

Before moving to the effects of sleep loss on indicators of sleepiness and alertness, it is necessary to understand characteristics of human alertness in various states of wake, sleepiness, and sleep.

2.3 CHARACTERISTICS OF HUMAN STATES OF ALERTNESS

Variations in brain activity reflect various states of alertness from wake to sleepiness or to sleep. In the human brain a complex interaction between cortical neurons and sub cortical 'pacemakers' underlies synchronization of postsynaptic potentials and hence rhythmic activity (Tononi, 2004). The Electroencephalogram (EEG) represents variations in the accumulation of postsynaptic potentials of cortical nerve cells measured at the scalp via electrodes (Olejniczak, 2006). The EEG is known to be one of the most predictive and reliable physiological indicators of sleepiness and alertness, and can reflect various states of brain activity from alert to sleepy, to being fast asleep. In fact, the EEG is often regarded as the "gold standard" to identify these states of arousal (Cluydts et al., 2002; Johnson et al., 2011; Lal & Craig, $2001_{(b);}$ Papadelis et al., 2007). The periodic rhythms in EEG are conventionally described by their frequency (Hz or cycles/sec) and their amplitude (μV, microvolts).

A range of EEG frequencies from 0.3 Hz to 70 Hz, have been measured in psychophysiological studies (Niedermeyer, 2005). Sleep-related EEG activity is typically observed between 0.1 and 30 Hz (Colrain, 2011). Four frequency components are conventionally obtained from EEG recordings, because they can be visually determined from the electroencephalogram and because they correspond to shifts in underlying brain state; delta (δ; 0-4 Hz, 20-200 μV), theta (θ; 4– 8 Hz, 10 μV), alpha (α; 8–13 Hz, 20-200 μV), and beta (β; 13–30 Hz, 5-10 μV) (Colrain, 2011; Jap, Lal, Fischer, & Bekiaris, 2009; Lal & Craig, $2001_{(a);}$ Niedermeyer, 2005). Of these frequency bands, alpha and beta are known as 'fast wave' activities, while theta and delta are 'slow wave' activities (SWA) (Colrain, 2011; Lal & Craig, $2001_{(a)}$). Alpha EEG is recognized in the electroencephalogram as a rounded or sinusoidal wave with amplitude of less than 50 microvolt which occur predominantly

over the posterior regions (occipital cortex) of the scalp during relaxed wakefulness and during early sleep onset (Berger, 1929; Lal & Craig, 2001(b); Niedermeyer, 2005). The EEG beta is associated with increased alertness and arousal (Eoh, Chung, & Kim, 2005), and attenuates during sleepiness (Jap et al., 2009; Lal & Craig, 2001(a)). The EEG sigma band, in the range of alpha and beta activities, is an additional band representing the discrete EEG morphology known as sleep spindles (Colrain, 2011). Sleep spindles are defined as a group of rhythmic waves in the 12–14 Hz range that progressively 'grow' in amplitude before gradually decreasing in amplitude (a waxing and waning of the amplitudes) across a period of 0.5 to 3 s (De Gennaro & Ferrara, 2003; Dijk, 1995; Himanen, Virkkala, Huhtala, & Hasan, 2002). The K-Complex wave, a very distinctive negative sharp waveform followed by a positive wave for total duration of more than 0.5 s, is another discrete EEG feature indicative of sleep onset (De Gennaro & Ferrara, 2003).

The EEG frequencies change from low amplitude high frequency activity to high amplitude low frequency activity during progression from wakefulness to deep sleep. In other words, EEG follows a characteristic progression from alpha to theta, K complexes, spindles and slow-wave activity (SWA) respectively. EEG frequencies are presented in Figure 2.6. This progression is mostly about "Sleep EEG" with less known about the distinct features of "Wake EEG" associated with increasing (or decreasing) sleepiness in the same way as Sleep EEG. The wake EEG spectrum should be monitored and interpreted to differentiate sleepiness from the alert wakefulness.

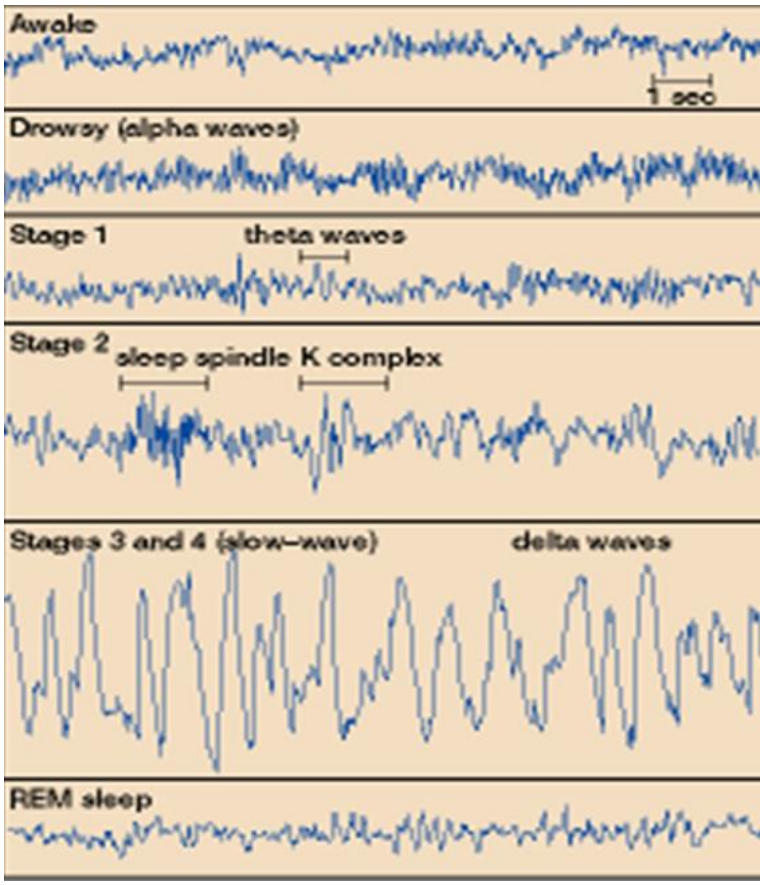

Figure 2.6. EEG frequencies (adopted from McGrath, 2010) .

The interpretation of the EEG spectrum is conventionally conducted by two methods; visual scoring (typically used in clinical diagnostic environments) and spectral analysis.

The first application of visual scoring of polysomnography (PSG; simultaneous measurement of electroencephalogram, electro-oculogram and electromyogram) to identify sleep states dates back to the 1930s (Silber et al., 2007). The current method of visual scoring (R&K), was published by Rechtschaffen & Kales (1968) to interpret human EEG sleep. Since then the R&K visual scoring criteria have been extensively used in sleep research as the standard classification of the arousal states that differentiate from wake from sleep, and differentiate the stages within sleep. According to the original R&K method, the major 'stages' of sleep include wakefulness, Non Rapid Eye Movement (NREM) sleep and Rapid Eye Movement

Sleep (REM). NREM sleep includes four sleep stages (1, 2, 3, and 4), while REM sleep comprises tonic REM and phasic REM states. In 2004, the American Academy of Sleep Medicine (AASM) commissioned the AASM Visual Scoring Task Force to review the R&K scoring system. This review resulted in several changes. As an example, the AASM renamed Stage 1 as N1, Stage 2 as N2, Stages 3 and 4 as N3 and REM sleep as R. The most significant change was the combination of Stages 3 and 4 into Stage N3 (these two stages were previously differentiated only by the proportion of observed 'slow waves' within each 30 s epoch of sleep). The revised scoring was published in 2007 as The AASM Manual for the Scoring of Sleep and Associated Events (Colrain, 2011; Iber, Ancoli-Israel, Chesson, & Quan, 2007). Visual scoring of the EEG depends strongly on the personal experience, training and calibration of the scorer (with typically poor inter-rater and within-rate reliability) and is also time-consuming.

The R&K and the AASM visual scoring systems have both been developed for clinical purposes to characterize human wakefulness and sleep. However, both systems have important conceptual gaps in terms of characterizing sleep onset. In particular, this approach poorly characterizes the transition from wakefulness, to drowsiness, and then to sleep (the sleep onset period).

Power spectral analysis (PSA) is an alternative quantitative approach to the description and interpretation of EEG data. This method is based on signal processing approaches (Welch, 1967). The Fast Fourier Transform (FFT) identifies signal amplitude for each frequency during 30 s epochs and quantifies the overall power trends in the EEG data (Ktonas & Gosalia, 1981). Using FFT the absolute power (μV^2), relative power (%), and mean frequency (Hz) within each frequency component in a given time domain (30 s epochs) can be determined. The *absolute power* of an EEG frequency band is the integral of all of the power values within its frequency range, while the *relative power* (RP) is the percentage of the absolute power in each frequency band relative to the sum of absolute powers of the four frequency bands (Yuvaraj et al., 2014). The different stages of sleep have been explained in more details as follows:

2.3.1 **Sleep**

NREM sleep typically comprises 75-80% of the total sleep time of healthy sleepers (with some changes in proportion across the lifespan). Stage 2 comprises 45-60% of the total sleep time, and typically starts after 10-12 min of Stage 1 sleep. During Stage 2 (N2) the maximum spindle frequency activity (SFA), power has been observed in 12-15 Hz which may intermittently co-appear with K-complex waves (De Gennaro & Ferrara, 2003). Small numbers of delta waves (0.5-4 Hz) may appear in the EEG, but eye movements (EOG) and muscle activity (EOG) decline (Natesan et al., 2006).

Stages 3 and 4 (N3), also known as delta sleep, slow wave sleep (SWS), or deep sleep, account for 15-20% of total sleep time (Natesan et al., 2006). Increased power density in the delta frequency, often known as slow wave activity (SWA), is a prominent feature of slow wave sleep (Dijk, 1995; Lal & Craig, $2001_{(b)}$). SWA, known as a hallmark of sleep intensity (Achermann & Borbély, 1998; Kecklund & ÅKerstedt, 1992), has a homeostatic regulation (Aeschbach & Borbely, 1993; Colrain, 2011; Ferrara & De Gennaro, 2011).

Rapid Eye Movement (REM) sleep compromises 20-25% of sleep duration (Aeschbach & Borbely, 1993; Natesan et al., 2006; Rosenthal, 2006).The first REM sleep typically starts 60-90 min after onset of NREM sleep (Natesan et al., 2006; Rosenthal, 2006), with cyclic episodes of REM sleep becoming more frequent later in the sleep period. Differentiating human Stage 1 sleep from REM sleep can be difficult due to similar amplitudes of occipital alpha power in the EEG during both sleep states (15–20 μV) (Cantero & Atienza, 2000). However, during REM sleep alpha activity in frequencies from 7.8 to 8.6 Hz yields higher power values and beta activity is lower as opposed to wakefulness and Stage 1 sleep (Cantero & Atienza, 2000; Jap et al., 2009). Figure 2.7 illustrates the EEG during different sleep stages. Characteristics of these sleep stages as defined by the two standard methods (R&K and the AASM) are presented in Table 2.1.

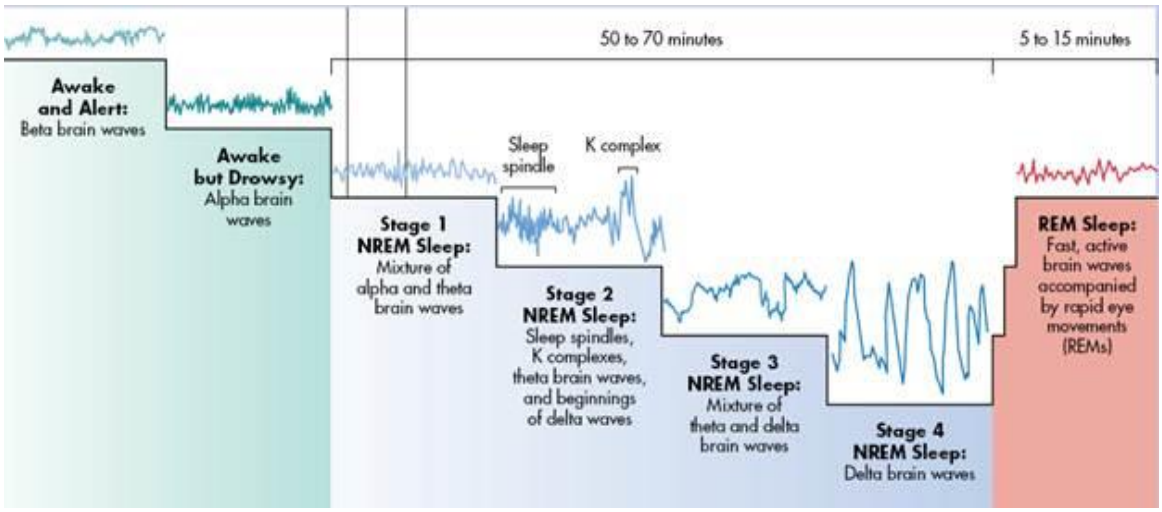

Figure 2.7. Human arousal states from awake to REM sleep (adopted from Ternopil State Medical University).

Table 2.1 Comparison of characteristics of sleep stages as defined by two standard methods proposed by Rechtschaffen and Kales and AASM

Sleep scoring method	Sleep/wake stage	EEG	EOG
Rechtschaffen and Kales	Relaxed wakefulness	Alpha activity (8-13 Hz) and/or a mixed frequency activity with low voltage	Rapid eye movement and rapid eye blinks
Rechtschaffen and Kales	NREM sleep Stage 1	Diminished alpha activity, appearance of low voltage mixed frequency activity. The highest activity is in theta frequencies (4-8 Hz)	*SEMs
AASM	N1	Intrusion of theta rhythm into an EEG epoch	Slow eye movements
Rechtschaffen and Kales	NREM sleep Stage 2	Appearance of sleep spindles and K-complexes. Occasional appearance of delta waves (0.5-4 Hz)	Lack of SEMs
AASM	N2	Mixed frequency theta activity, K-complexes, sleep spindles	
Rechtschaffen and Kales	Slow wave sleep (SWS)	NREM sleep Stage3: Moderate amount (> 20% but < 50% of a 30 s period) of high amplitude (> 75 microwatts), slow wave activity (0.5-2 Hz)	Lack of SEMs
		NREM sleep Stage 4: Large amount (> 50% of 30 s period) of high amplitude (> 75 microwatts), slow wave activity (0.5-2 Hz)	Lack of SEMs

AASM	N3	Significant large (>75 μV) delta frequency waveforms	
Rechtschaffen and Kales	REM sleep	Stage tonic: Desynchronized EEG (Low-voltage, mixed frequency activity with slow alpha, 1-2 Hz less than alpha activity in wakefulness) with small amount of theta	
		Stage phasic: Low-voltage, mixed frequency activity with slow alpha (1-2 Hz less than alpha activity in wakefulness) and theta	Fast eye movement in all directions
AASM	R	Mixed frequency, theta and beta EEG activity	Rapid eye movements

*SEMs: slow eye movements

2.3.2 **Wake**

Wake is an arousal state associated with desynchronized low voltage mixed frequency (predominantly beta) activity and synchronized alpha activity (8-13 Hz), rapid eye movement and blinks, and high muscle tonus levels (Colrain, 2011; Natesan et al., 2006; Rosenthal, 2006). Alpha activity varies during wakefulness among well-rested individuals, and between eyes open or eyes closed conditions. During resting wakefulness with eyes closed, alpha typically shows higher activity while during active wakefulness with eyes open and resting position, alpha usually shows low levels of activity (Cote, Milner, Osip, Baker, & Cuthbert, 2008; Ferreira et al., 2006).

2.3.3 **Sleepiness**

The conventional 'stages' of sleep (described above) are not always necessary, nor sufficient, to describe the state or presence of sleepiness (Eoh et al., 2005; Lal & Craig, $2001_{(b)}$). Sleepiness is mostly induced by conditions such as sleep loss, delayed or advanced bedtime (circadian disturbance or circadian desynchrony), sleep fragmentation (Otmani et al., 2005), variations in sleep quality, individual state and trait differences in sleep propensity, together with interacting factors that impact on arousal such as alcohol, drugs and other medication (Lowden et al., 2009).

Sleepiness, at one extreme, can correspond to the onset of Stage 1 sleep. Stage 1 comprises 3-8% of overall sleep time and mostly occurs during the transition from wakefulness to NREM sleep, and sometimes during transitions from arousals to other stages of sleep (Natesan et al., 2006; Rosenthal, 2006). These transitions are not as gradual as perceived subjectively (Trinder, J, Waloszek, Woods, & Jordan, 2012). Characteristics of Stage 1 are repeated alternation between alpha activity (relaxed wakefulness) and low voltage mixed frequency activity with the highest activity in theta frequencies (4-8 Hz) indicative of early sleep onset (Gora, Colrain, & Trinder, 1999), the occurrence of slow rolling eye movements, the reduction in tonic EMG, the appearance of vertex sharp waves (50-200 milliseconds) at the end of Stage 1 (Natesan et al., 2006; Rosenthal, 2006), and finally the emergence of sleep spindles which initially are accompanied by vertex waves (Yeo, Li, & Wilder-Smith, 2007).

There are some inconsistencies in the description of alpha activity during sleepiness between researchers. Various studies have found that in the early sleepiness state alpha activity increases when compared with the lower alpha activity observed during alert wakefulness with the participant's eyes open (Åkerstedt & Gillberg, 1990; Eoh et al., 2005; Liu, Hosking, & Lenné, 2009; Niedermeyer, 2005; Otmani et al., 2005; Torsvall & ÅKerstedt, 1987). Lal & Craig ($2001_{(a)}$) reported that, at the beginning of sleepiness, alpha rhythm may attenuate for a few seconds, reappear again, and continue this fluctuation for a few minutes until these 'trains' of alpha waves finally disappear. In contrast, Santamaria (1987) and Jap (2009) reported a decrease in the amplitude of the occipital alpha rhythm. In spite of these discrepancies, it is generally believed that sleepiness is characterized by the disappearance of alpha activity (Lal & Craig, $2001_{(b)}$).

Theta activity, observed as distinctly slower EEG waves, provides another index of vigilance level in the waking electroencephalography similar to alpha activity (Campagne et al., 2004). The EEG theta activity can occur during a variety of mental states including sleep onset (Lal & Craig, $2001_{(b)}$), and Stage 1 sleep (Eoh et al., 2005). Progressive increase in spectral power in the theta frequency band is related to the presence of sleepiness (Åkerstedt & Gillberg, 1990; Lal & Craig, $2001_{(b);}$ Otmani et al., 2005). However, Liu et al. (2009), were of the opinion that theta activity is associated only with more 'severe' sleepiness. Increments of theta also correlate with some deficits in subjective sleepiness and alertness such as impaired concentration, distracted thoughts, and longer lapses (Orzeł-Gryglewska, 2010).

Vertex sharp waves are unique to sleepiness and appear at the end of Stage 1 and the beginning of Stage 2 sleep, either as an isolated phasic event or as repetitive sharp waves (De Gennaro & Ferrara, 2003; Yeo et al., 2007). Vertex sharp waves are indicators of inhibitory mechanisms preventing the processing of sensory stimuli during sleep onset (Peszka & Harsh, 2002), and facilitate the initiation and maintenance of sleep (Yeo et al., 2007).

Some researchers have introduced different staging criteria to describe sleepiness. Santamaria & Chiappa (1987) classified the EEG of sleepiness into four distinct phases as follows:

1. A transitional phase: between awake and absence of alpha, this phase contains microsleeps (Lal & Craig, 2002),
2. A combination of transitional and post-transitional phases, with characteristics of either transitional or post-transitional phases,
3. A post-transitional phase (immediate EEG epochs after disappearance of alpha, early Stage 1 of sleep, this phase contains microsleeps as well (Lal & Craig, 2002),
4. An arousal phase (awakening from sleepiness).

Hori et al. (1991; 2001) and Tanaka et al. (1996) followed this classification with the introduction of a broader concept known as the sleep onset period (SOP). The SOP refers to the transition phase from sleepy wakefulness (sleepiness) to unresponsive sleep. In this understanding, the SOP contains the whole Stage1 sleep, but overlaps into both wakefulness and Stage 2 sleep by R&K criteria (Tanaka, H, Hayashi, & Hori, 2000; Yeo et al., 2007). The classification of different stages of SOP is shown in Table 2.2. The EEG Stages 1 and 2 in this classification are equivalent to Stage W (wakefulness) in R&K criteria. The EEG stages 3 to 8 correspond to Stage 1 sleep and EEG stage 9 in this classification is equivalent to Stage 2 sleep in the R&K criteria. The latter researchers also defined some new criteria to identify EEG stages during sleep onset.

Table 2.2 Characteristics of different stages of sleep onset period (Tanaka, H et al., 2000)

Stage of sleepiness	**Characteristics**
EEG stage1(alpha wave train)	Appearance of a chain of alpha activity with amplitude of 20 *µV
EEG stage 2 (alpha wave intermittent, A)	Attenuation of alpha to a train comprising at least 50% alpha activity with a minimal amplitude of 20 µV
EEG stage 3 (alpha wave intermittent, B)	Progressive alpha attenuation to a train comprising less than 50% alpha activity with minimal amplitude of 20 µV
EEG stage 4 (EEG flattening)	Progressive suppression of alpha activity even at amplitudes less than 20 µV
EEG stage 5 (Ripples)	Suppression of low voltage theta wave burst, between 20 µV and 50 µV in the absence of vertex sharp wave
EEG stage 6 (Vertex sharp wave solitary)	Appearance of the first well-defined vertex sharp wave
EEG stage 7 (Vertex sharp wave train or burst)	Presence of at least two well-defined vertex sharp waves
EEG stage 8 (Vertex sharp wave and incomplete spindle)	Simultaneous presence of at least one well-defined vertex sharp wave and one incomplete spindle with 0.5 s duration and amplitude between 10 µV and 20 µV
EEG stage 9 (Spindles)	Presence of at least one well defined spindle with at least 0.5 s duration and 20 µV amplitude

*µV= microvolts

Some studies have reported high correlations between subjective sleepiness and EEG Alpha and Theta activities, and have confirmed that drivers can be aware of their sleepiness prior to critical driving events (Horne, James A & Baulk, 2004; Howard et al., 2014; Williamson, Ann, Friswell, Olivier, & Grzebieta, 2014). However, these studies have not reported if changes in Alpha and Theta EEG activities occurred prior to drivers' perceived sleepiness. According to the aforementioned sleepiness classification (Tanaka, H et al., 2000), Delta activity together with vertex sharp waves, which are related to behavioural changes and a subjective feeling of ''vagueness'', start to appear at the late part of sleep onset from stage 6 onwards (the end of Stage 1 sleep; (Finelli, Achermann, & Borbély, 2001; Hori, T et al., 1991; Tanaka, H et al., 2000; Yeo et al., 2007). This implies that changes in Alpha and Theta activities could represent the start point of sleepiness, and that subjective sleepiness appears at some point after primary EEG changes in Alpha and Theta activities. The point at which drivers perceive their sleepiness is of great importance in that they mostly rely on their feeling of sleepiness before taking measures to combat their sleepiness.

Overall, sleep and sleep onset, are not simple, homogenous, or monotonous processes. Instead, the processes are continuous, very dynamic, and complex. Therefore, superficial (visual) features of sleepiness need to be considered along with 'deeper' facets such as changes in spectral power in the EEG bands. Electrophysiological methods can be used to objectively and reliably measure a shift in alertness and sleepiness, and may provide some indices of relevance to driving skills. More specifically, these findings suggest that alpha and theta activity could be hallmarks of sleepiness (and of sleep onset) during driving studies. It could be expected that a dominance of alpha EEG activity during driving would be replaced by theta EEG dominance at the onset of sleep and that this change in EEG would appear earlier than subjective perceptions of sleepiness.

The next sections explain the main sources of sleepiness particularly sleep loss, and their effects on drivers' sleepiness in all levels.

2.4 SLEEP DEPRIVATION

Sleep deprivation is the main reason for driver's sleepiness and in this context refers to insufficient sleep periods (totally or partially) due to early morning awakening, extended wake, and sleep fragmentation. Early wakeup is more prevalent among shift workers who drive in the early morning (Smith, S. et al., $2009_{(b)}$) while extended wake is a behaviour often observed in samples of long-haul and heavy vehicle drivers (Horne, J.A & Reyner, 2001).

A study among more than 1500 non-professional drivers revealed that 30% of non-professional drivers were habitually sleep deprived for 1 hour and 25% of them have a sleep debt of 2 hours (Carter, Ulfberg, Nyström, & Edling, 2003). Additionally, drivers are more confronted with chronic partial sleep deprivation than just one night total sleep loss (Otmani et al., 2005).

Both acute total sleep deprivation and chronic partial sleep deprivation impact on neurobehavioral function during subsequent wake time. Chronic partial sleep deprivation (e.g. consecutive nights of insufficient or limited sleep) may cause greater deficits than that of short term acute sleep loss. This appears to be related to the accumulative aspects of sleep debt. One explanation for this effect was provided by Cote et al. (2008), such that the brain may be able to compensate for the effects of short periods of extreme sleep loss (e.g. 24 h), but be unable to sustain that compensation for longer durations. Data on sleep-related crashes is consistent with an impact of chronic-partial sleep loss on safety. In some studies, the sleep-related crash rates were found to be 3 to 5 fold higher among drivers habitually sleeping less than 5 hours per night (Connor et al., 2002; Stutts et al., 2003). In another study (Otmani et al., 2005), there was no change in the crash rate after one night of partial sleep deprivation (3 h) but from the second night to the fifth night of partial deprivation, this rate significantly increased. (Matthews et al., $2012_{(b)}$) in a 28-h daytime forced desynchrony protocol for one week, regardless of time of day or amount of time awake, found that chronic moderate or severe sleep restriction significantly increased the standard deviation of lateral position ($F_{2,1923} = 95.81$, $p < 0.001$).

Attempts have been made to specify the minimum sleep time necessary for preventing chronic sleep related performance deficits. One week partial sleep

restriction to 5 hours per night was found to linearly increase sleepiness, impairment of mood and performance "lapses" (Dinges et al., 1997). A minimum 6 hours sleep per night was subsequently identified as an adaptable sleep threshold (Cote et al., 2008; Drake et al., 2001).

Contrary to Drakes's (2001) statement of a minimum sleep threshold of 6 hours and contrary to *the core sleep theory* (Van Dongen et al., 2003), some researchers have reported that maintaining sleep time at 6 hours per night over several days may decrease performance . Similarly, progressively impaired psychomotor vigilance performance, impaired working-memory performance, and impaired cognitive throughout performance in both 4-h and 6-h (time in bed per night) conditions has been observed, although in both conditions slow wave activity was conserved (Orzeł-Gryglewska, 2010; Van Dongen & Dinges, 2005; Van Dongen et al., 2003). These deficits were comparable to those found after 1 to 2 days of total sleep deprivation. The latter authors proposed that approximately 8 hours of sleep was the minimum sleep necessary for unaffected performance (15.84 ± 0.73 h wake time per day).

In addition to the amount of sleep deprivation, the stage of the restricted sleep is important. Based on *the core sleep theory*, it was primarily believed that if slow wave sleep (Stages 3 and 4 of NREM sleep) remained uninterrupted, chronic sleep deprivation would not affect performance (Van Dongen et al., 2003). In contrast, Karni et al. (1994) found that selective deprivation of REM sleep impaired performance on a visual discrimination task, whereas selective deprivation of SWS did not impair the performance on this task.

Currently, it is well established that chronic sleep loss or fragmentation of sleep results in impaired performance, mainly in cognitive functions, attention and working memory, comparable to those of short-time total sleep deprivation (Orzeł-Gryglewska, 2010). Current peak consensus for the sleep needs of an adult suggest that 7–9 hours of sleep are appropriate to support optimal health in adults (Watson et al., 2015).

2.4.1 **Effects of sleep loss on objective outcomes of sleepiness**

Waking electroencephalogram (EEG)

Sleep deprivation appears to exert local effects on the brain, rather than global effects (Ferreira et al., 2006). According to *the local use dependent theory*, the pre-frontal cortex (PFC) is the most active region of brain during wakefulness. Sleep is a crucial recovery opportunity for this region. Therefore, it is not surprising that the pre-frontal cortex is more vulnerable to sleep deprivation than are other brain areas (Couyoumdjian et al., 2010; Ferreira et al., 2006). Reduction of brain activity in pre-frontal cortex has consistently been shown following total sleep deprivation (Cote et al., 2008).

Increased activity in EEG measures of alpha (Gillberg, Kecklund, Göransson, & Åkerstedt, 2003; Lowden et al., 2009), or both alpha and theta bands have been validated against increased sleepiness and are known as indicators of sleepiness (Åkerstedt & Gillberg, 1990; Horne, J.A & Reyner, 1996; Kecklund & Åkerstedt, 1993; Torsvall & ÅKerstedt, 1987). Studies of EEG characteristics among drivers are limited and have been mostly concerned with alterations in alpha and theta bands (Papadelis et al., 2007). Alpha and theta activities have been studied as absolute or relative power. The relative band ratio is a unit-less value between 0 and 1 and represents the relative ratio of the power of each frequency band against the total frequency power for the EEG frequency bands (delta: 0.5–4 Hz, theta: 4–8 Hz, alpha: 8–12 Hz, beta: 12–30 Hz, and gamma: 30–40 Hz) (Papadelis et al., 2007).

In a daytime 1.5 hour simulated driving task in non-sleep-deprived participants, increased activities in relative alpha and theta power were observed at the end of driving task with increasing driver sleepiness (Zhao, Zhao, Liu, & Zheng, 2012).

In a morning (8 a.m) 50 min simulated driving task, after a night of sleep deprivation and a dose of caffeine, EEG alpha (α: 8–13 Hz), EEG theta (θ: 4–8 Hz) and EEG (α+θ)/β; increased gradually during the drive, while EEG beta (β: 13–22 Hz) and β/α decreased. Additionally, index β (13–22 Hz) increased immediately after crashes (losing the control of the car) and gradually decreased over time (Eoh et al., 2005).

In an on-road nocturnal driving task for one hour followed by one night total sleep loss an increase in relative powers in the delta and alpha bands, but a decrease in the relative power in beta and gamma frequency bands (in central and parietal areas)

were observed (Papadelis et al., 2007). Additionally, the extended wake periods exerted an increasing effect on EEG alpha activity, reflecting decreased cortical arousal (Lal & Craig, $2001_{(b)}$).

Waking electrocardiogram (ECG)

The electrocardiogram (ECG) describes the electrical activity of heart activity. Heart activity is continually modulated by the sympathetic and parasympathetic nervous systems. The most obvious index of heart activity is the heart rate. The reciprocal of the heart rate is called inter-beat interval, which is time interval between individual beats (typically between successive R waves in the QRS complex (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014).) observed in the ECG. This interval is also called as inter-beat interval, beat-to-beat interval, or R-R interval. The term Heart Rate Variability (HRV) refers to changes in the inter-beat intervals, indicating changes in the balance between sympathetic and parasympathetic activity (Michail, Kokonozi, Chouvarda, & Maglaveras, 2008).

HRV is commonly calculated from R-R intervals by two methods: frequency domain (Power spectral analysis) and time domain (statistical operations) (Ergün, Demirci, Nurlu, & Komürcü, 2008). Power spectral analysis of HRV is commonly used to calculate the sympathetic and parasympathetic activity of the autonomous nervous system (Schaffer, Hensel, Weigand, Schüttler, & Jeleazcov, 2014). In this method the R-R interval is converted to sum of sinusoidal functions of frequencies and amplitudes using the Fast Fourier Transform (FFT) (Ergün et al., 2008). The power spectrum represents the amplitude of heart rate variability in three forms of LF, HF, and LF/HF (Ergün et al., 2008). The LF is the low-frequency (slow rhythm, from 0.04 to 0.15 Hz) heart rate variability, and is understood to be controlled by both sympathetic and parasympathetic nervous systems. The LF heart rate variability represents wakefulness characteristics such as higher sympathetic and/or lower vagal activity. HF is the high-frequency (fast rhythm, 0.15 to 0.4 Hz) heart rate variability, and is primarily controlled by the parasympathetic system. HF HRV may provide an index associated with ‘sleepy’ characteristics, such as lower sympathetic and/or higher parasympathetic and vagal activity (Baharav et al., 1995; Michail et al., 2008).

The sympathovagal balance between these two components is defined as LF/HF ratio (Baharav et al., 1995).

Sleep-related studies in driving settings have found inconsistent changes in ECG measures. For instance, there was no significant alteration of heart rate variability during a one hour on-road trip after one night of total sleep loss (Papadelis et al., 2007). However, in another study sleep deprived drivers showed a lower LF/HF and lower LF values (Michail et al., 2008). In a 2-hour simulated drive during daytime increasing heart rate was positively correlated to increased sleepiness, but there was no change in HRV indices of sleepiness during the drive (Wijesuriya, Tran, & Craig, 2007). In a daytime driving experiment a 1.5-hour simulated drive resulted in a decreased LF HRV and an increased HF HRV (Zhao et al., 2012).

Studies show that mean RR during wake period is lower than sleep episodes and during SWS is greater than wakefulness before sleep onset. (Boudreau, Yeh, Dumont, & Boivin, 2013)

Heart rate (beat/minute) decreases during sleepy driving (Borghini, Astolfi, Vecchiato, Mattia, & Babiloni, 2014), particularly night time driving (Lal & Craig, $2001_{(a)}$). For instance, in a long time night-time driving for 9.5 hours with total sleep loss, heart rate decreased (Riemersma, Sanders, Wildervanck, & Gaillard, 1977). In another simulated drive for 120 min, there was a decrease in heart rate during driver's sleepiness (Liang, Yuan, Sun, & Lin, 2007). Since these studies have been conducted during sleep deprivation the changes in heart rate might reflect circadian variation in HR not the effect of sleep loss alone. There was no significant alteration of heart rate variability during one hour on-road driving at night time after one night total sleep loss (Papadelis et al., 2007).

Cognitive performance

Studies on the mechanism of impairments in cognitive performance have revealed that the cognitive functions subserved by the pre-frontal cortex (PFC) may be particularly sensitive to sleep loss (Couyoumdjian et al., 2010). During sleep loss attenuation in arousal extends to posterior region after rapid and progressive linear decreases in arousal in the pre-frontal cortex (Cote et al., 2008). In this stage some

behavioural deficiencies start to appear, such as impaired attention, inefficient information processing, reduced decision-making capability, impaired communication and language skills, divergent thinking, as well as impaired memory, motor function, mood and wake status (Couyoumdjian et al., 2010; Drake et al., 2001; Jones & Harrison, 2001; Papadelis et al., 2007; Smith, S. et al., $2009_{(b)}$).

The magnitude of impairment in cognitive performance from sleep loss seems to be dependent on some factors such as the type of task performed, the type of performance test (Cluydts et al., 2002; Horne, J.A & Wilkinson, 1985), and the severity of sleep restriction (Otmani et al., 2005).

The majority of performance tests, including simple task performance tests (such as the Psychomotor Vigilance Task; PVT), and complex task performance tests (e.g. executive function), are sensitive to sleep loss (Cluydts et al., 2002; Couyoumdjian et al., 2010; De Gennaro et al., 2007; Smith, S. et al., $2009_{(b)}$). The PVT (visual or auditory) appears to be a sensitive performance test, in that the tonic alertness (vigilance or sustained attention) is the component of the attention network most affected by sleep loss when compared to the other components of cognition (Lim & Dinges, 2008; Papadelis et al., 2007).

In the PPVT, reaction times are sorted into the following categories:

Type 1: representing false responses (responses made prior to stimulus presentation) (Tarvainen et al., 2014), Type 2: correct responses (Tarvainen et al., 2014), Type 3: lapses representing the responses slower than 500 milliseconds after the stimulus onset on the PVT (Arnedt, Geddes, & MacLean, 2005; Kim et al., 2001; Lim & Dinges, 2008; Martella et al., 2011; Papadelis et al., 2007; Smith, S. et al., $2009_{(b)}$), and Type 4: very slow responses.

Some other variables are typically extracted from PPVT data including, mean reaction time, standard deviation of reaction time from correct responses (as measure of performance variability); and percentage of false responses (as measures of performance accuracy) (Loh, Lamond, Dorrian, Roach, & Dawson, 2004; Sforza, Haba-Rubio, De Bilbao, Rochat, & Ibanez, 2004), and mean reciprocals of reaction times (1/RTs, seconds $^{-1}$) as the reaction speed (Sforza et al., 2004). These variables are listed in Table 5.3. It should be noted that attention lapses are discrete

phenomena from prolonged lapses (most often understood to reflect microsleeps). There are some differences between these two types of lapses. Firstly, attention lapses can wax and wane in seconds, more frequently than prior assumptions of fluctuations over minutes or hours, while prolonged lapses last longer than attention lapses (3-15 s) (Lim & Dinges, 2008). The fact that sometimes sleepy drivers have had a crash during wakefulness with open eyes(Jackson et al., 2013), confirms that changes in human vigilance level can be very rapid. Secondly, attention lapses are not only modulated by sleep loss (homeostatic drive), but also by circadian drive (Dinges et al., 1997; Martella et al., 2011; Ting, Hwang, Doong, & Jeng, 2008; Van Dongen & Dinges, 2005), and most frequently occur across the circadian nadir (Lim & Dinges, 2008; Van Dongen & Dinges, 2005), while prolonged lapses are only seen in sleep-deprived participants and not among well-rested individuals (Welsh, Thomas, & Thome, 1998).

Sleep loss has been found to elicit significant impairments on both visual and auditory PVTs including increased attention lapses and prolonged lapses.

In a study involving a severe sleep loss (62 hours of continuous wakefulness) an increasing effect of hours of wakefulness was observed on the number of lapses and mean reciprocals of reaction time (Lamond et al., 2008).

The relationship between attention lapses (measured by PVT) and higher crash risk rates has been repeatedly demonstrated (Arnedt et al., 2005). For instance, attention lapses from sleep loss have been found to be associated with both lane drifting (Jackson et al., 2013; Philip et al., $2005_{(a)}$) and road crashes on a driving simulator (Dinges et al., 1997; Ting et al., 2008).

2.4.2 **Effects of sleep loss on subjective outcomes of sleepiness**

All forms of sleep loss (acute or chronic partial sleep loss) have been shown to lead to an increased subjective sleepiness (Cluydts et al., 2002; De Gennaro et al., 2007; Otmani et al., 2005; Van Dongen et al., 2003; Zhou et al., 2012). Liu, et al. (2009) reported that an increase in sleepiness score (on the KSS) from a rating of 5 (*neither alert nor sleepy*) to a rating of 9 (*very sleepy, great effort to stay awake*), dramatically raised the risk for a major lane departure. Nevertheless, subjective

perception of sleepiness has been typically found to be less sensitive to sleep loss than are the corresponding neurocognitive measures (Finelli et al., 2001; Hori, T et al., 1991; Tanaka, H et al., 2000; Yeo et al., 2007). A larger gap between subjective and objective sleepiness at higher levels of sleepiness has been observed (Cluydts et al., 2002; Dinges et al., 1997; Drake et al., 2001; Zhou et al., 2012). For instance, Van Dongen, et al. (2003) observed that at the end of 14 days of chronic sleep limitation, the participants reported that they only felt slightly sleepy, while in contrast their PVT scores were far more deteriorated.

2.4.3 **Effects of sleep loss on driving performance measures of sleepiness**

A variety of driving performance outcome measures, mostly a combination of several variables have been used to measure driver performance when sleepy. These measures include lane departures (lane excursion or inappropriate lane crossing), the standard deviation of lane position (SDLP), the standard deviation of lateral position, the minimum time to lane crossing (TLC), the number of line edge crossings, mean amplitude of steering wheel movements (SWM), the standard deviation of steering wheel angle (SDSWA), steering wheel movements count, mean speed, standard deviation of speed, and other metrics.

Lane keeping behaviour (ability of drivers to maintain a stable lane position (Atchley & Chan, 2011) is measured by mean lane position, the standard deviation of lane position (SDLP), the total number of centre line crossings and total number of road edge excursions.

Lateral position, or the driver's ability to track the lane centre, reflects road tracking errors or ‘weaving’ and has also been found to be very sensitive to sleepiness. Sleepy drivers have repeatedly exhibited larger variations in lateral position (Arnedt et al., 2005; Arnedt, Wilde, Munt, & MacLean, 2001; Lenné, M.G, Triggs, & Redman, 1998).

The standard deviation of lane position (SDLP), refers to the driver's ability to maintain a straight path (driver precision), although not necessarily a specific position relative to the lane centre (Boyle, Tippin, Paul, & Rizzo, 2008). This variable is the most frequently studied outcome measure of driving performance

(Sandberg, D., Akerstedt, Anund, Kecklund, & Wahde, 2011$_{(a)}$). Sleepiness has shown to increases deviation from the average position of the vehicle (Atchley & Chan, 2011; Desmond & Matthews, 1997; Liu et al., 2009). Increase in the standard deviation of lateral lane has been repeatedly reported in nocturnal simulated driving tasks with total sleep loss (Phipps-Nelson, Redman, & Rajaratnam, 2011) or extended wakefulness (Anund et al., 2008$_{(a)}$) as well as in daytime studies with partial sleep loss (De Valck & Cluydts, 2001).

Lane departure or inappropriate lane crossing (ILC) could vary from minor incidents (e.g. part of the car crossing a lane boundary) to major incidents (e.g. the entire car crossing a lane boundary). According to epidemiological findings, 65% of sleep-related crashes occur after an inappropriate lane crossing (Sagberg, 1999). Minor departures occur more than major ones (Sagberg, 1999), but both types of departures appeared to be important indicators of driver impairment (Liu et al., 2009). For example, in a randomized cross-over study the total number of inappropriate line crossings increased by 8 cases after sleep restriction (Philip et al., 2005$_{(a)}$). Regarding specific types of lane departure, if any part of the tyre straddles the road way centre line a centre line crossing is counted. If the tyres leave the road edge line in the driver's direction (left edge line) a road edge excursion is counted (NCSU Human Factors and Ergonomics (HFE) Area, 2011). Increase in the number of lane infractions is an indicator of impaired attention (Liu et al., 2009) or fatigue (Atchley & Chan, 2011; Oron-Gilad & Shinar, 2000).

Variations in the mean vehicle speed appear to reflect the ability of the driver to control their speed during microsleep episodes (Boyle et al., 2008; Risser, Ware, & Freeman, 2000). However, speed choices also reflect other aspects of driving behaviour, road type, and traffic characteristics (Sandberg, D. et al., 2011$_{(a)}$). Many drivers tend to slow down when experiencing sleepiness or impaired vigilance, particularly at night time (Lenné, M. G et al., 1997). An increase in speed fluctuations (deviation from the posted speed limit) seems to be a common feature across studies (Arnedt et al., 2001; Brookhuis, Waard, & Fairclough, 2003; Campagne et al., 2004; Lenné, M. G et al., 1997). Higher speed deviations in driving after sleep loss have been more specifically associated with the driver's inability to pay attention to both the road scene and the speedometer simultaneously (Jackson et

al., 2013). Accordingly the number of speeding errors (speed exceedance) could be one marker of sleepiness (Campagne et al., 2004).

Gravitational forces (G-forces) are important outcome measures of driving performance and are measures of variation in vehicle acceleration from delayed braking, fast starts and hard right-hand or left-hand turns (Simons-Morton, Zhang, Jackson, & Albert, 2012). These sudden accelerations increase the risk of losing control of vehicle, decrease the available time for both the driver and other road users to react to the hazardous situations in time (Bagdadi & Várhelyi, 2011). A correlation of 0.6 has been observed between G-Force event rate and crashes and near crashes rate among teenage drivers over a period of three years (Simons-Morton et al., 2012). Despite the importance of these indices, G-forces are mainly known as physical facets of driving and the effects of sleep loss on the nature and magnitude of changes in G-forces are not well known yet, particularly in car drivers.

Steering wheel related outcome measures have also examined by sleep deprivation. Normally drivers maintain a steady course on the road by make minor steering adjustments. Both number and amplitude of steering wheel movements (SWM) increase during sleepiness (Brown, I. D., 1997; Lal & Craig, $2001_{(a)}$). Sleepy drivers fail to correct their vehicle heading, and consequently make larger and more rapid movements of the wheel to keep the trajectory bring it back onto the lane. Therefore, large SWM's (6–10°) or extremely large SWM's (more than 10°) have been associated with increased driver sleepiness (Atchley & Chan, 2011; Brown, J. D., 1994; Thiffault & Bergeron, $2003_{(b)}$).

In a night-time simulated drive for 2 hours following a 4-hour sleep loss the preceding night, there were no significant effects of sleep deprivation on either mean amplitude of small steering wheel angle (between 0.5° and 5°) or frequency per minute of small steering wheel angle. In this study smaller angles indicated higher sleepiness levels (Otmani et al., 2005). Additionally, a greater standard deviation of steering wheel angle shows increased fatigue (Atchley & Chan, 2011).

In the most comprehensive study of driver performance by Forsman et al. (2013) the researchers drew 87 different metrics of driving performance from the literature and examined those variables in two simulated driving studies on 41 subjects. They found that of the 87 metrics just two - steering variability and lane variability -

captured most of the variance in performance. Lane variability in particular was correlated with night-time subjective sleepiness.

Lane position outcome measures have also been examined in combination with steering-based variables to acquire complementary information about sleepy drivers (Friedrichs & Yang, 2010). Berglund (2007) in a study on 22 participants on a truck simulator found that of 17 driving performance outcome measures a linear combination of steering wheel direction reversals (the number of cases the driver changed the direction of the steering wheel over a time interval), vehicle path deviations (the area of the vehicle deviation) and standard deviation of lateral position showed the highest sensitivity to sleepiness (Cluydts et al., 2002).

2.5 OTHER CONTRIBUTORS TO SLEEPINESS

2.5.1 **Circadian pressure for sleep**

Based on *the two-process model of sleep-wake regulation*, the neurobehavioral impairment from sleep loss (homeostatic drive) accumulates throughout the day based on the circadian drive. Therefore, sleepiness is more severe at certain times of day after sleep deprivation (Vakulin et al., 2007). For instance, driving performance on measures such as steering movement, speed, standard deviation of speed, and reaction time, are poorer during nights and the afternoons (Lenné, M. G et al., 1997; Reimer et al., 2007).

The interactions between circadian rhythm and homeostatic drive for sleepiness have been studied in forced desynchrony protocols through de-coupling the circadian phase from sleep times by enforcing non-24 hour ‘days’. Under these conditions, the clock times of sleep and wake change over consecutive days, and the phase relationship between sleep episodes and the circadian rhythm also vary. This approach allows researchers to examine driver performance at different combinations of prior wake and circadian phase (Zhou et al., 2012). It is important to consider the impairment in alertness and driving performance from the circadian drive in sleepiness studies.

2.5.2 **Time-on-task**

The time-on-task effect refers to attenuation of performance across the course of a task. According to the report of Horne & Reyner (1995), all the early morning sleep-related crashes involving truck drivers occur within the first two hours of driving (Horne, J.A & Reyner, 2001). Borb (1999) also found that an increase of just 10 minutes in driving duration, in conjunction with short prior nocturnal sleep (< 6 h), was associated not only with increased rear-end collisions but also with increased single-car crashes.

A variety of studies, have examined the effect of driving duration, sometimes combined with sleep loss, on driver objective outcome measures of sleepiness. Simulated driving studies have shown that increased driving duration results in increased EEG activity in both alpha (Eoh et al., 2005; Schier, 2000), and theta band (Kecklund & Åkerstedt, 1993), higher numbers of short (1 s) alpha bursts (Boyle et al., 2008; Eoh et al., 2005; Kecklund & Åkerstedt, 1993), and higher numbers of short theta bursts (Kecklund & Åkerstedt, 1993). Otmani et al (2005) also reported that during simulated driving both alpha and theta EEG power increased in response to increased driving duration. Extended driving time has resulted in higher eye blink rates and slower eye blink in other studies (Papadelis et al., 2007; Sandberg, D et al., $2011_{(b)}$).

Simulated driving studies have shown that increased driving duration results in higher ratings of subjective sleepiness (Arnedt et al., 2005; Kecklund & Åkerstedt, 1993; Lowden et al., 2009; Sandberg, D et al., $2011_{(b);}$ Ting et al., 2008). Moreover, time-on-task effects can be observed in increased impairment of driver's cognitive performance. In a simulated driving study, median brake reaction times during the last 10-minute period of a 90-minute session were found to be 0.31 s longer than those in the first 10 minutes. This difference equates to an additional 8 metres in stopping distance when travelling at 100 km/h (Schmidt et al., 2009).

Some studies have examined the effect of driving duration on driving performance specifically (Arnedt et al., 2005). For instance, a study by Thiffault & Bergeron ($2003_{(b)}$), demonstrated that as driving duration increased drivers made fewer small steering wheel movements (1-5 ^{o}), but made a greater number of larger steering wheel movements (6-10 ^{o}). Thiffault and Bergeron ($2003_{(b)}$) attributed this difference

to the inability of the drowsy driver to detect small lane deviations due to sleepiness. A similar relationship between steering wheel movements and time-on-task was reported by Otmani et al. (2005). Additionally extended time of driving increases the standard deviation of the lateral position (Otmani et al., 2005; Sandberg, D et al., 2011$_{(b);}$ Ting et al., 2008), higher rates of edge line crossings (Otmani et al., 2005), increases in vehicle speed, decreased driver awareness of pedestrians (Ranney, Simmons, & Masalonis, 1999), and decreased steering performance (Van der Hulst, Meijman, & Rothengatter, 2001).

Consistent with some of the data above and contrary to the general belief that long driving hours affect driver performance. Philip, et al. (2005$_{(a)}$), could not find any substantial effect of the duration of driving on performance and sleepiness. They attributed this discrepancy to the brief 'active breaks' that they had included within their paradigm, and so their findings may not apply to sustained driving without such breaks.

There is no consensus on the start point of significant time-on-task effects. In spite of previous thoughts that time-on-task effects only appears after a minimum task duration of 30 minutes, it has been confirmed that sleep-deprived subjects may exhibit time-on-task effects after just a few minutes of performance (Lim & Dinges, 2008). This may particularly be the case in simulated driving studies, during which sleepiness generally appears faster than real on-road driving conditions (Arnedt et al., 2005), perhaps due to differences in motivation or other factors. In an attempt to provide general guidance for drivers, some researchers have scored the performance of drivers in different durations of driving, and reported that the optimum duration of safe highway driving is approximately 80 min at a constant speed of 60 km/h (Nilsson, Nelson, & Carlson, 1997; Ting et al., 2008). However, there is no good evidence to support this recommendation.

2.5.3 **Fatigue from work demands**

Fatigue from work demands such as multiple jobs or long work shifts, contributes to sleepiness among 50% of drivers (Di Milia, 2006). Long shift lengths not only result in higher fatigue from the workload per se, but also result in extended wakefulness. The frequency of sleep-related crashes among shift-workers engaging in more than

60 hours of work per week is more than 3.7 times more than other workers (Stutts et al., 2003). Barger et al (2005) found an increased rate of sleep-related crashes amongst medical interns working with extended work shifts of more than 80 hours per week in the hospital. They reported that motor vehicle crashes and near-miss incidents after an extended shift were respectively 2.3 and 6 times higher when compared with a non-extended shift. These findings are consistent with data from a previous survey by Heslegrave et al. (2000) on the driving behaviour of miners changing from 9-hour to 12.5-hour shifts with a 30-min commute. They pointed out that a switch to a 12.5-hour shift resulted in more drivers falling asleep at the wheel and greater likelihood of having near misses when compared with the former 9-hour shift (Di Milia & Bowden, 2007).

2.5.1 **Individual differences in vulnerability to sleep loss**

There appears to be great inter-individual difference in resistance to some sleep-related deficits such as sleepiness and mood alterations (Åkerstedt et al., 2002$_{(b);}$ Ohayon, Smolensky, & Roth, 2010; Otmani et al., 2005), decrements in vigilance, disturbance of working memory, and impairment of executive function(Van Dongen, Baynard, Maislin, & Dinges, 2004(b)). A study on sleep-related crashes highlighted that only 5% of truck drivers account for 26% of sleep-related crashes. Indeed 20% of them were involved in 60% of crashes (Hanowski, Wierwille, & Dingus, 2003). These differences are known to be associated with individual variations in EEG activity patterns during waking, personality traits(Van Dongen et al., 2004(b)), such as extroverted and tension-prone personality (Lal & Craig, 2001$_{(a);}$ Thiffault & Bergeron, 2003$_{(a);}$ Verwey & Zaidel, 2000), sensation seeking (Martin, S. B. et al., 2007; Thiffault & Bergeron, 2003$_{(a)}$), external locus of control (Verwey & Zaidel), eveningness, neuroticism, rigid sleeping habits, difficulty in overcoming drowsiness, proneness to internal desynchronization (Costa, 2003), and some negative mood states including anger, anxiety, confusion and low levels of vigour (Lal & Craig, 2001$_{(a)}$).

Considerable variations have been revealed between individuals on their waking EEG. Studies have shown that the alpha and sigma frequency activities can be considered individual trait-like characteristics. Additionally, during sleep and

NREM-REM-NREM sleep transitions, there are large regional frequency-specific EEG differences between people. These regional EEG differences are reliably unique for each person and allow individuals to be distinguished from each other with a high probability (92%). The uniqueness of these EEG patterns is one of the genetically-determined traits of human beings (Ferrara & De Gennaro, 2011).

Likewise, the magnitude of psychomotor performance impairment after 36 h sleep loss varies substantially between individuals, but the performance profile is known to be stable for each person (Van Dongen & Dinges, 2005). Inter-individual differences have also been observed in working memory performance, but to a lesser extent than the differences seen in psychomotor vigilance performance (Van Dongen & Dinges, 2005).

The most common personality trait studied in vigilance tasks such as driving is related to the extroversion–introversion dimension (Thiffault & Bergeron, 2003$_{(a);}$ Verwey & Zaidel, 2000).

Extroverts are 'stimulus-hungry', and make more compensatory effort when confronted with low levels of stimuli. Hence they tend to demonstrate a poorer performance on monotonous driving tasks (Brocke, Tasche, & Beauducel, 1997; Thiffault & Bergeron, 2003$_{(a)}$). Sensation seeking is general term for individuals with some personality dimensions such as a tendency to do risky or adventurous tasks, experience seeking (ES; seeking of arousing experiences and novel environmental stimuli), disinhibition (DIS; behaviours of nonconformity through social and sexual experiences) and boredom susceptibility, an aversion to monotonous and repetitive experiences (Martin, S. B. et al., 2007; Pintrich & Maehr, 2004; Thiffault & Bergeron, 2003$_{(a)}$).

The implications of personality traits on different performance measures of drivers have been already examined. For instance, extroversion and boredom personalities had an increasing effect on departure from the road due to falling asleep, whereas disinhibited-honest subjects were more likely to cross solid lane markings even without falling asleep (Verwey & Zaidel, 2000). Another study revealed that sensation seeking, particularly the experience seeking (ES) dimension, may be an indicator of increased variance in steering wheel movements (in monotonous roads).

This study indicated a higher prevalence of falling asleep at the wheel among high sensation seekers (Thiffault & Bergeron, 2003$_{(a)}$).

Given the importance of the individual differences, they need to be quantified, controlled, or manipulated in future studies.

2.5.2 **Monotonous conditions**

Monotonous and boring tasks such as driving appear to be more impaired by sleep loss than are other types of task (Papadelis et al., 2007). Most studies regarding the effects of sleep loss on driving performance have been undertaken in driving simulators. The simulator environment appears to induce an earlier and more pronounced decline in driver performance when compared with real driving environment (Cluydts et al., 2002), mainly due to the more monotonous or predictable driving conditions. Monotony refers to a situation with constant or highly repetitive stimulus (Thiffault & Bergeron, 2003$_{(b)}$). Monotonous driving on long and straight roads with little visual stimulation intensifies, or unmasks, drowsiness (Gilad & Ronen, 2008). Motorway routes, highways and rural roads, roads with few turns and no road signs or stop lights, may be more monotonous than urban routes in simulated driving (Arnedt et al., 2005; Boyle et al., 2008; Reimer et al., 2007). According to the findings of Thiffault (2003$_{(b)}$) driver sleepiness is clearly observable in the first 20 minutes of driving under monotonous conditions. Some of the symptoms observed included increased number of lane departures (Arnedt et al., 2005; Gilad & Ronen, 2008), longer minimum times taken to lane crossing (TLC) (Boyle et al., 2008), and higher standard deviations of vehicle speed (Arnedt et al., 2005; Reimer et al., 2007).

2.5.3 **Age of drivers**

There is a large variability across the spectrum of drivers in terms of their perceptual, cognitive, and physical abilities (Horberry & Inwood, 2010). Some of these variations occur in very loose association with age (Wong, Smith, Sullivan, & Allan, 2014).

Older drivers have shown to get less sleepy than younger drivers at night (Lowden et al., 2009; Philip, 1999). This could partly be explained by differences in activation of the hypothalamic–pituitary–adrenal (HPA) axis which results in higher mean nocturnal cortisol levels among older adults. Cortisol underlies increased brain activity in the sigma and beta EEG bands, and activity in these bands is associated with higher vigilance level and shorter sleep (Lowden et al., 2009; Van Cauter, 1996). Another reason for differences in sleepiness could be the lack of high alpha activity (representing higher sleepiness) among older people (Lowden et al., 2009). Findings of a night time simulated driving (Campagne et al., 2004) revealed increased alpha activity among both the young and middle aged group, but not the elderly group (60–70 years). Therefore, they could not find any significant correlation between alpha activity and incidents of running off the road among older drivers. Instead, driving errors in this group was observed during severe sleepiness (during increased EEG theta spectral power). This could be a neurophysiological change (less EEG alpha generated) or a measurement issue (less EEG alpha observed).

There are some differences in cognitive performance in response to sleepiness between younger and older drivers. Sleep restricted to 4 or 6 hours of nocturnal sleep has shown cumulative deficits in neurobehavioral performance among younger drivers (Van Dongen et al., 2003). Younger drivers (less than 25 years) although demonstrating faster simple reaction times after normal sleep (Philip, 1999; Philip et al., 2004; Quimby, Maycock, Carter, Dixon, & Wall, 1984; Smith, S. et al., $2009_{(b)}$), show slower reaction times than do older drivers after 8 h of driving (Philip, 1999), or when driving after sleep loss (Philip et al., 2004; Smith, S. et al., $2009_{(b)}$). In spite of demonstrating faster simple reaction times, novice drivers normally exhibit slower hazard perception latencies (reaction time to a potential hazard) than do more experienced drivers, and this difference increases with increased age (Smith, S. et al., $2009_{(b)}$). Faster or more efficient hazard perception by older drivers may contribute to higher resistance to sleepiness (Smith, S. et al., $2009_{(b)}$).

The adverse effects of sleep loss on young drivers' performance are discussed in a systematic review in Chapter 3.

2.5.4 **Health status**

A number of health-related factors can also impact on individual's trait sleepiness, and on the responses to sleep loss, restriction or disruption. For example, people experiencing a range of psychiatric disorders may exhibit reduced heart rate variability. At the same time, many psychoactive medications themselves reduce heart rate variability. This has implications for the utility of HRV-based indices of sleepiness (or arousal) in these populations. Other medical diseases may raise the risk of sleepiness (Craig & Hancock, 1996; Wijesuriya et al., 2007). Some health problems such as obstructive sleep apnea syndrome (Boyle et al., 2008), some medical disorders, large body mass indices (BMI) more than 30 kg/m² (Smith, M. R., Cullnan, & Eastman, 2008), and use of medicines and illicit drugs, are each known to contribute to driver sleepiness.

Generally, exogenous and endogenous contributors to sleepiness are rarely isolated and tend to co-occur while driving. The major underpinning factors include sleep loss (acute or chronic sleep loss due to early morning wake up, extended wakefulness or sleep disturbances), mistiming of sleep-wake with circadian rhythm (shift work, international travel (jetlag), social choices (social jetlag) and phase delay in adolescence), time-on-task fatigue from work demands, age, environmental conditions, health status, and individual differences in vulnerability to sleepiness. These factors induce microsleep episodes and result in decreased neurobehavioral and cognitive performance in both on-road and simulated driving tasks (Jackson et al., 2013; Martella et al., 2011). Therefore, development of an efficient countermeasure for sleepiness while driving is of great importance in transportation safety.

2.6 SUMMARY AND IMPLICATIONS

2.6.1 **Summary of findings of the literature review**

The literature review was conducted with the purpose of understanding sleepiness as part of human sleep-wake regulation, problems of sleepy driving, effects of sleep deprivation on driver sleepiness, other contributors to driver sleepiness, the gaps in

the existing knowledge of the effects of sleepiness on driving, particularly in young drivers.

The available literature suggests that human sleep and wake are part of arousal states that could be predicted by a number of sleep regulation models. Although these models are not directly concerned with human sleepiness, they are of great importance in understanding the factors involved in the regulation of sleep-wake and hence sleepiness. According to the basic model, the *two-process model of sleep-wake regulation,* the interaction between homeostatic and circadian drives results in human sleep and wake, with the homeostatic drive increasing after 16 hours of wake period and the circadian drive regulated by time of day (as an indirect effect of light), with minimum effect around 10 a.m. Based on *the ultradian-process of sleep-wake regulation,* a cyclic rhythm (ultradian rhythm) within the NREM and REM sleeps is regulating these two stages. Based on this model the selective sleep loss leads to elimination of different stages of sleep. The waking up earlier than usual (REM-sleep deprivation) seems to impair performance more than extended wake (reduction of NREM sleep). Based on *the three-process model of human sleep-wake regulation,* there is a third drive to sleep, *sleep inertia* that is a lower alertness level after awakening persisting for a few hours (up to 4 hours).

The literature review revealed some important facts about the type and severity of sleep deprivation among drivers. Practically, drivers experiencing chronic partial sleep deprivation over more than one are more affected than those with acute sleep deprivation. A considerable proportion of non-professional drivers (33%) suffer from one hour sleep deprivation (7 hours of sleep) (Carter et al., 2003), while a minimum 8 hours sleep per night is needed to prevent degradation of performance due to sleepiness. Drivers younger than 24 years old are more sensitive to sleep loss than older drivers, partly due to their physiological differences and are over represented in sleepiness-related crashes.

Based on the reviewed studies, monitoring sleep-wake time is crucial to ensure compliance of participants with sleep deprivation regime. The best and the most reliable method is Actigraphy. Most studies have monitored sleep-wake times for 1 to 2 weeks.

In addition to the abovementioned findings, the review pointed out some factors that are not included in sleep-wake regulation models but are contributing to sleepiness. These factors had some major implications in the protocol of this research program with the experimental study designed to manipulate or eliminate them.

The literature highlights the need for taking a multidimensional approach to measure sleepiness, in that sleepiness might affect a variety of neurobehavioral outcomes to different extents. This is important in that sleep deprivation might degrade subjective sleepiness to a lesser extent than objective levels. The literature also shows that subjective perception of sleepiness (increasing EEG delta activity) occurs after starting objective sleepiness (increasing alpha and theta activity). These findings highlight that subjective outcomes of sleepiness are not reliable alone and all types of subjective and objective sleepiness and driving performance outcome measures need to be measured together.

In-vehicle outcomes, comprising large numbers of outcomes, could be measured via on-road experiments or by simulated driving experiments. On-road studies involve more limitations in that they have more difficulties in measuring EEG-related outcome measures and are not as accurate as simulated experiments.

2.6.2 **Implications of the literature review**

Factors that could be manipulated

Since sleepiness is part of the same sleep-wake cycle in *the two-process model of sleep-wake regulation* the same two drives for sleep are inducing sleepiness while transitioning from wake to sleep. The sleep loss, whether from a long wake period or from sleep restriction, strengthens the homeostatic pressure for sleep and increases sleepiness. This indicates that in order to measure daytime sleepiness from sleep loss alone, the homeostatic part of sleepiness should be included (i.e. by reducing time in bed) and the sleepiness from the circadian drive should be excluded by measuring sleepiness at the times of day with minimum circadian drive for sleep (around 10 am).

Taking the *ultradian model of sleep-wake regulation* to induce as much sleepiness as possible, it is best to restrict sleep time to the NREM stage only and eliminate the REM sleep by awakening participants in early morning.

Based on *the three-process model of sleep-wake regulation* and in order to avoid the confounding effect of *the sleep inertia*, a minimum time of 4 hours needs to be considered between the wake-up time and the time of measuring sleepiness.

Considering the effects of these three models, an early morning wake-up time no later than 6 am seemed to meet all the considerations of homeostatic and circadian drives for sleepiness, sleep inertia, and selective REM sleep deprivation.

Based on mechanisms of regulating the circadian rhythm of human sleep-wake by light, it is important to let the participants be exposed to daylight at the interval between the wake-up time and measurement of sleepiness. This insures that daylight attenuates the circadian drive for sleepiness to its minimum levels by the time of measuring sleepiness from homeostatic drive alone.

Based on the two-process model of sleep-wake regulation the length of sleep loss is of importance and determines the severity of sleepiness from the homeostatic drive. Since one-third of non-professional drivers are experiencing sleep debt of 1 hour, a minimum 1 hour of sleep deprivation (awakening 1 hour earlier) was determined to induce the realistic mild sleepiness and a minimum of four consecutive days were considered to induce the chronic sleep deprivation.

Considering the higher sensitivity of young drivers to sleepiness, drivers between 18 to 25 years were selected as the sampling group for the experimental study.

Factors that could not be manipulated

The literature showed that there are other contributors to sleepiness that are not included in the computational models of human sleep-wake or alertness regulation. These models only apply to mean group data and generally are not able to predict individual-level effects (Åkerstedt & Folkard, $1995_{(b);}$ Cluydts et al., 2002; Van Dongen, $2004_{(a)}$). Some of these factors such as monotony, stress, drugs and participant health status (Åkerstedt & Folkard, $1995_{(b)}$)could be identified and be eliminated by setting some relevant exclusion criteria. However, some of them,

particularly inter-individual differences (age, driving experience, personality) could not be easily traced. Therefore, the contribution of these factors to driver's sleepiness could be eliminated by using a repeated-measures study design.

2.6.3 Gaps in the knowledge of effects of sleep loss on drivers' alertness and performance

Even though chronic sleep loss is more realistic and the more often experienced type of sleep loss in drivers' daily lives, most studies have examined the implications of acute total or acute partial sleep loss on human sleepiness, alertness and performance. In particular, the effects of sleep loss on young drivers' performance are not well understood. Current computational models predicting sleepiness from sleep loss are also predominantly based on data from studies of acute total sleep loss (Åkerstedt et al., 2008). As a result, the broader effects of sleepiness conferred by chronic partial sleep loss (Van Dongen, $2004_{(a)}$) are less predictable. Therefore, a systematic review of the effects of sleep loss (including chronic sleep loss) on young drivers' performance was conducted and is presented in Chapter 3:.

This literature review (Chapter 2) did not include the alerting effects of light and caffeine. A review of the alerting effects of light and caffeine on sleepy drivers in the driving context was conducted and is presented in Chapter 4.

The literature also revealed no evidence of the effect of commercially available light and caffeine on young drivers' alertness and performance after chronic partial sleep loss. Therefore, those effects were examined in an experimental study (presented in Chapter 5:).

Chapter 3: A Systematic Review and the GRADE Rating Analyses of the Evidence on the Effects of Sleep Loss on Young Drivers' Performance

The effects of sleep on young drivers' performance are systematically reviewed and the quality of the body of evidence is graded in this chapter. As a systematic review can be regarded as scientific investigation in itself (Mulrow, 1994), it has been presented here as a separate chapter.

This chapter begins with a definition and description of the benefits of systematic reviews and meta-analyses (Section 3.1). The rationale for conducting this specific systematic review is provided in Section 3.2. The methods of conducting the systematic review in this research, the GRADE rating analysis, and the results of the review and GRADE analysis are explained in Section 3.3 and Section 3.4, respectively. Finally, the conclusions are provided in Section 3.5.

3.1 DEFINITION AND BENEFITS OF SYSTEMATIC REVIEWS AND THE GRADE RATING ANALYSIS

Systematic reviews are a rigorous type of literature review (Mallett, Hagen-Zanker, Slater, & Duvendack, 2012) driven by the principles of evidence-based medicine, and particularly by the methods developed and promoted by the Cochrane Collaboration (Higgins & Green, 2008). Based on the Cochrane Collaboration definition, a systematic review is "a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review" (Fineout-Overholt, Melnyk, Stillwell, & Williamson, 2010).

Systematic reviews have evolved to identify, critically assess, and synthesise the research already conducted in a field, with particular emphasis on the inclusion of

high-quality quantitative and/or qualitative evidence. This can be done to make the results from a sometimes large and diverse literature available in a reliable, succinct and usable format (Fineout-Overholt et al., 2010; Korhonen, Hakulinen-Viitanen, Jylhä, & Holopainen, 2013; Mallett et al., 2012).

While traditional narrative reviews are subject to the bias and impressions of the individual reviewers (Mulrow, 1994), the values and benefits of systematic reviews are now well-established. This approach enables the researcher to capture all the available literature, addresses systematic errors of bias and increases the reliability, accuracy and confidence in conclusions across the body of evidence addressing a specific question (Fineout-Overholt et al., 2010). It is typical in the literature for there to be inconsistencies in the direction and magnitude of effects between studies (Mulrow, 1994). Such inconsistencies can arise from different study designs, different eligibility criteria for participants, different definitions and measurement methods for exposure, and different interventions. This approach is now recognized beyond the Cochrane Collaboration, with many journals either dedicated to, or accepting of, systematic reviews.

A meta-analysis is the statistical combination of results from at least two studies to generate estimates of the effect of the intervention with greater precision (Korhonen et al., 2013; Mulrow, 1994). Meta-analysis is not always included in a systematic review (Fineout-Overholt et al., 2010), but systematic reviews of randomised controlled trials (RCTs) which have adopted a meta-analysis of results, are regarded as the best (level 1) evidence (Korhonen et al., 2013). It should be noted that because of insufficient studies of sleep deprivation paradigms and driving tasks with shared outcome measures and methodological differences in sample size, it was not possible to conduct a meta-analysis in this study. Therefore, only the directions of findings were compared, followed by a GRADE rating analysis of quality of the body of evidence.

3.2 RATIONALE FOR CONDUCTING A SYSTEMATIC REVIEW

Young drivers appear to be at a higher risk of road crashes than are older drivers (Campagne et al., 2004; Horne, J.A & Reyner, 1995; McCartt et al., 1996; Ting et

al., 2008). The increased risk of being involved in a traffic crash for drivers younger than 24 years has been estimated to be 2 to 10 fold higher when compared to other age groups (Åkerstedt et al., 2001; Sagaspe, P et al., 2010). Young drivers also comprise a greater proportion of driver fatalities. For example, young drivers comprise only 13% of the Australian population, but comprise 22% of driver fatalities (Bureau of Infrastructure Transport and Regional Economics (BITRE), 2013). The quantification of the effects of sleep deprivation on young drivers' performance has important implications for determining the potential benefit of the alerting effects of countermeasures, such as exposure to light. For this purpose, it is crucial to understand the effects of sleep loss on young drivers' performance. There are currently about 150 papers published on the effects of sleep loss on drivers' sleepiness outcomes. A small proportion of the existing literature has examined the effects of sleep loss on young drivers' performance-related outcomes specifically. There are also substantial inconsistencies between findings in the existing literature due to different study designs, different sleep deprivation regimens, different outcome measures, different definitions of similar outcome measures of driver performance, and variable measurement methodologies. These discrepancies have made it difficult to draw reliable conclusions about the directions and magnitude of the above-mentioned effects. To the best of the researcher's knowledge there is only one systematic review, published in 2001, examining the effect of driver sleepiness on crash rates (Connor, Whitlock, Norton, & Jackson, 2001). To date there are no narrative reviews or systematic reviews available on the effects of sleep loss on drivers' performance, particularly on the performance of young drivers.

Given the higher sensitivity of young drivers to sleep loss, and current uncertainty about the nature, directions and magnitude of the effects of sleep loss on young drivers' performance, a systematic review and GRADE rating analysis on the effects of sleep loss on young driver's performance were undertaken.

3.3 METHOD OF SYSTEMATIC REVIEW

Different methods for the conduct and transparent reporting of systematic reviews have been recommended since QUOROM (Quality Of Reporting Of Meta-analysis; (Moher et al., 1999), the first guidelines for reporting meta-analyses, were developed

in 1999. The PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analysis; (Moher, Liberati, Tetzlaff, & Altman, 2009) was introduced in 2005 as an evolved version of the QUOROM guidelines. The PRISMA statement comprises a checklist of 27 items that should be reported in systematic reviews to reflect the findings of the review explicitly, following a four-phase flowchart from identification to inclusion of studies in the review. A novel series of statements, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines, were introduced from 2011 to 2013 in a series of 15 papers published in the Journal of Clinical Epidemiology (Andrews et al., 2013(1); Andrews et al., 2013(2); Balshem et al., 2011; Brunetti et al., 2013; Guyatt et al., 2011(1); Guyatt et al., 2011 (2); Guyatt et al., 2011(5); Guyatt et al., 2011(7); Guyatt et al., 2011(6); Guyatt et al., 2011(4); Guyatt et al., 2013(2); Guyatt et al., 2011(8); Guyatt et al., 2011(3); Guyatt et al., 2013 (3)). These guidelines can be adopted as part of systematic reviews to assist in summarising the findings, to grade the quality of evidence provided by the findings, and to summarise the magnitude of the effects of interventions (Guyatt et al., 2011(1)). A wide range of potential clinical applications were considered in developing the GRADE guidelines and this approach is used to guide reviews in public health (Dijkers, 2009). Because of its wide range of applications, the GRADE approach was chosen to inform the approach of this review. GRADE provides guidelines to develop a research question, to select the important outcome measures in terms of their benefits for consumers, and to evaluate the quality of evidence for those outcome measures. This system is applicable for grading both high quality and low quality evidence (and is the first approach that downgrades or upgrades the quality of evidence (Dijkers, 2009). The primary literature review (Chapter 2:) identified diversity in study approaches and probable quality in the literature, so this framework was used to formalize that impression.

The current systematic review was undertaken according to the PRISMA and GRADE guidelines. Based on these guidelines, a review protocol was developed that included the following explicit steps:

1. Development of the research question
2. Definition of scope, inclusion and exclusion criteria
3. Systematic search for information

4. Screening and selection of eligible studies based on PRISMA flowchart
5. Review of selected reports based on the GRADE guidelines
6. Grading the quality of the body of evidence using the GRADE criteria
7. Summarising effect sizes using GRADE guidelines

3.3.1 **Research question**

The research question was first developed using the PICOS approach described in the PRISMA guidelines (Moher et al., 2009). In this approach, the research question is ideally constructed after consideration of Population, Intervention, Comparator (control), Outcomes and Study design elements. The research question that evolved from the PICOS approach was:

What are the effects of sleep loss on young drivers' performance outcomes?

Young drivers in this review were considered to be adults aged from 18 to 24 years. Selection of this age range was based on conventional classification of young adults in sleep and circadian studies. The term 'sleepiness' refers to the term 'fatigue' as well. Fatigue in this review refers to an undistinguishable feeling of sleepiness and tiredness due to a long drive or monotonous driving conditions (Phillips, 2015). However, due to the lack of a standard definition for sleepiness and fatigue, we have used them interchangeably to address the need for sleep. All forms of sleepiness or fatigue, induced by acute or chronic sleep loss, including extended wake duration, early morning wakeup (sleep limitation), sleep fragmentation or sleep disturbance were included in the review. Driver performance outcomes of interest included both cognitive and in-vehicle performance outcomes in real on-road or simulated driving experiments. All forms of study design including Randomised Control Trials (RTCs), observational studies such as longitudinal, quasi-experimental, correlational experiments, and cross-sectional studies, were reviewed. Only peer-reviewed original research papers were included in the review to ensure the quality of the body of evidence. Since all study designs were included in the review, the study design was not reflected in the research question. This research question dictated the search strategy to be taken.

3.3.2 **Scope of review**

The review included only peer-reviewed papers of any design published from 2004 to 2014 that examined the effects of any type of sleep loss on young drivers' cognitive and driving performance outcome measures from any on-road or simulated driving paradigm (see Section 3.2). Only papers published in English were considered because translation of information from other languages may increase the risk of bias (Patil & Davies, 2014). Additionally, exclusion of non-English literature has little effect on estimation of effects (Jüni, Holenstein, Sterne, Bartlett, & Egger, 2002).

3.3.3 **Inclusion criteria**

Papers were eligible for review if they met all criteria as described in Table 3.1.

3.3.4 **Systematic search for information**

A comprehensive Boolean/Phrase search was conducted from 27 July 2014 to 12 August 2014 for papers within electronic data bases including: PsycINFO (via EBSCOhost), PsycARTICLES (via EBSCOhost), MEDLINE (via EBSCOhost), Science Direct, ProQuest Psychology journals database, Web of Science, Scopus, Ergonomic Abstracts (via EBSCOhost), PubMed (via NCBI), Trip, CINAHAL (via EBSCOhost), Transportation Research Information Database, The Cochrane Library and EMBASE.

The following key words were included in the search statement: [("sleep depriv*" OR "sleep loss" OR "sleep limitation" Or "sleep restriction") AND ("sleepiness" OR drows* OR hypersomnol* OR "sleep onset" OR "excessive sleep*" OR "sleep propensity" OR fatigue* OR microsleep* OR alert* OR vigilance OR hypovigilan*) AND (driver OR simulator OR vehicle OR "commercial drivers" OR "professional driver" OR "driver performance" OR "truck driver" OR "bus driver")].

Table 3.1. Criteria for inclusion of papers in the systematic review

No	Inclusion Criterion	Description
1	Young participants	Participants were young (18-24 years old), healthy, non-professional and non-shift working car drivers who were free from sleep disorders
2	Sleepiness caused by sleep loss	Sleepiness was induced by sleep deprivation. This means that studies examining other forms of sleepiness without any prior sleep deprivation (e.g. time-on task fatigue or usual daytime sleepiness) were excluded from the study. However, studies that could not distinguish sleepiness caused by sleep loss from sleepiness (fatigue) from time-on task were included.
3	All forms of sleep loss	All forms of sleep loss acute or chronic sleep loss, including extended wake duration, early morning wakeup (sleep limitation), sleep fragmentation or sleep disturbance were identified as eligible.
4	Sleep loss as exposure	Sleep deprivation was the main exposure; studies examining the effect of other agents (e.g. light, Modafinil, caffeine, nap, rest, exercise, etc.) on sleep deprived subjects were excluded,
5	Driving performance as primary outcome measures	The primary outcome measures of interest were driver performance on either a driving simulator or real road; studies measuring driving performance in all forms along with other objective and subjective determinants of sleepiness were included. Studies on prevalence of

No	Inclusion Criterion	Description
		sleepy driving were excluded
6	Published in the last 10 years	Published between 1 January 2004 and 30 December 2014
7	All types of study design	There was no study design limitation to this systematic review. Therefore, all types of study design including RCTs, experiments, cross-sectional and observational studies were included
8	Only peer-reviewed	Only papers published in peer-reviewed journals were included
9	English language	Only papers published in English were included

Some data bases such as the Transportation Research Information Database, The Cochrane library and EMBASE do not utilise asterisk (*) within their search strategy. Therefore, the complete wordings of key words were substituted for searches within these databases.

From 7/12/2014 to 14/12/2014 all searches were updated to find all new papers published from 1/08/2014 to 31/12/2014. The precise search statements and limiters are presented in the Table 3.3.

Using filters in some databases, the findings were narrowed to only peer-reviewed papers published between 2004 and 2014. In some cases the journal websites were checked directly for verification of their peer-review processes. Search alerts were activated in some databases to automatically update the records. Bibliographic records of all identified papers were also examined to identify additional potential papers for inclusion.

3.3.5 **Screening and selection of eligible studies**

The selection of papers for review was undertaken as described by the search flow diagram in the PRISMA statement. Firstly, all studies retrieved from the databases or from examining the references were included. Secondly, after aggregating all records and removing duplicates, the title and abstracts of all papers were checked against the inclusion criteria. In the next phase, the full-text prints of the selected papers were assessed against the eligibility criteria, and the reasons for inclusion/exclusion of papers were documented. Finally, papers were selected after a discussion with other members of the research team, and a consensus method was used to make a decision in case of any discrepancy. Whenever possible, further information was sought from authors of the selected papers about their study.

3.3.6 **Review of selected reports using the GRADE**

Summarising the papers

Once the selection was completed, the important elements of studies were summarised and sorted by the outcome measures of interest. It should be noted that all items specified in GRADE (developed primarily for review of health and medical

literature) were not applicable to studies on road safety. Therefore, some important aspects of studies such as study design, sample size, participants' age range, sleep deprivation regime, driving conditions, and findings were considered for each outcome measure. In the next step, the important strengths and potential flaws of studies underlying the quality of each outcome were extracted and documented to assess the quality of the 'body of evidence'.

Grading the quality of body of evidence

In order to grade the quality of individual papers using the GRADE guidelines (Balshem et al., 2011), the applicable factors for downgrading or upgrading the quality score were identified as the grading criteria. Since GRADE is flexible and relies to some extent upon the judgment of the researcher, some other important downgrading and upgrading factors specific to the available data and sleep studies were also considered and added to these criteria. In the next step, based on the GRADE guidelines, a multi-step approach was used to grade the quality of the 'body of evidence' for each specific outcome. First the quality of each individual paper, and then then the quality of the body of evidence (all available papers), was determined for each given outcome.

Grading the quality of each individual paper

Firstly, it should be clarified that GRADE is an outcomes-based guideline. This means that the GRADE approach rates the quality of each paper, and then the whole body of evidence for a single outcome measure. The quality of each paper for a given outcome measure was assessed by adopting some GRADE criteria (downgrading and upgrading factors). This process involved deducting one point for downgrading factors and then by adding one point for upgrading factors as follows:

Firstly, the quality of papers was scored for their study design. Randomised control trials (RTCs) initially scored a rating of 'high-quality' while observational studies using longitudinal, quasi-experimental and correlational designs and cross-sectional studies were initially assigned a 'low-quality' score. Studies were then downgraded for the quality of findings for each outcome measure in light of factors such as study

limitations (risk of bias), imprecision (i.e. broad confidence intervals), inconsistency of results between studies, indirectness (caused by findings from similar population i.e. stroke instead of traumatic brain injury), and likelihood of publication bias (not publishing the study at all due to null or contrary findings). Risk of bias is considered a major factor for downgrading the quality of papers. Risk of bias refers to problems with "validity" or "internal validity" of the study. Different causes of risk of bias have been identified for RTCs and observational studies. Important contributors to risk of bias in observational studies include inappropriate inclusion/exclusion criteria for participants, flawed measurement of both exposure and outcome, and inappropriate control for confounders (Guyatt et al., 2011(1)).

Secondly, the quality of papers were upgraded if a large magnitude of effect on the outcome was reported, a dose response relationship was described, or some confounders were involved which acted to minimise the effects of the independent variable. A single quality score for each outcome measure for each paper was generated by adding all assigned points.

Finally, an Overall Grade Score (OGS) across the body of evidence (all papers reporting the same outcome measure) was derived (Guyatt et al., 2011(1)). The overall score was not simply an average of scores for each outcome across papers, but was based on the contribution of each paper to the quality of the body of evidence. For example, studies with larger sample sizes had a greater impact on the overall quality score (Guyatt et al., 2011(1)). Therefore, a special algorithm was developed to estimate the OGS of the body of evidence. This algorithm is explained in Section 3.4.7.

3.3.7 **Estimate of effect size**

Effect size refers to either of the strength of relationships or to the magnitude of differences described in the studies. The correlation coefficient (r) or regression coefficient (R), commonly reported as indices of association, are in fact measures of effect sizes. These coefficients can show the whole range of positive, zero, or negative relationships in a precise way, and are also coefficients that are independent of sample size. Most publications identified in this review reported effect sizes in an unstandardized way, for example, as a measure of difference in the original units (i.e.

a 0.4 second increase in reaction time after sleep loss). This is a measure of effect giving the actual difference; however, does not give any idea whether the difference represents a big, medium, or small effect. Ideally, these actual differences should be accompanied by standardised effect size measures to allow comparison of effects between studies. The standardized effect sizes are independent of what is being measured (measuring units) and are calculated by the same scale for all types of effect (Walker, 2008).

According to Cohen's rules of thumb for interpreting effect sizes (Cohen, 2013), a "small" effect size refers to a real effect observable through careful study. A "large" effect size is a substantial effect (big enough, and/or consistent enough) which can be easily observed. As an example, r = 0.1 conventionally represents a 'small' effect size, while r = 0.3 and r = 0.5 refer to a 'medium' and a 'large' effect size, respectively (Walker, 2008).

Table 3.2 represents some conventions for the description of different standardised effect sizes (Watson et al., 2015). Each paper was searched for estimates of effect size reported in any of these ways (Table 3.2). The reported effect sizes are presented in Table 3.7.

Table 3.2 Standardised effect sizes and their magnitudes (adopted from Watson et al., 2015)

Effect Size Metric	Use	Small	Medium	Large
r	Correlation	0.1	0.3	0.5
η^2	one-way Anova (regression)	0.01	0.06	0.14
η^2	Anova	0.02	0.13	0.26
omega-squared	Anova	0.01	0.06	0.14
Multivariate eta-squared	one-way MANOVA	0.01	0.06	0.14
Cohen's f	one-way an(c)ova (regression)	0.10	0.25	0.40
η^2	Multiple regression	0.02	0.13	0.26
κ^2	Mediation analysis	0.01	0.09	0.25
Cohen's f	Multiple Regression	0.14	0.39	0.59
Cohen's d	t-tests	0.2	0.5	0.8
Cohen's ω	chi-square	0.1	0.3	0.5
Odds Ratios	2 by 2 tables	1.5	3.5	9.0
Average Spearman rho	Friedman test	0.1	0.3	0.5

3.4 RESULTS

3.4.1 **Database search and data extraction**

Overall 369 records were found through the initial database search. One relevant paper was later identified by searching the references of selected papers.

Of the initial 370 records, 240 duplicates were removed. The titles and abstracts of the 132 remaining papers were then screened. Using the inclusion/exclusion criteria described in Table 3.1, a further 53 studies were excluded. The seasons for exclusion were: studies of professional drivers or shift workers (criterion 1), published in non-peer-reviewed journals (criterion 9), or review papers on the prevalence of sleepy drivers (criterion 5). From the 79 remaining records, 69 papers were excluded after assessing their full text, due to a primary focus on independent variables other than sleep deprivation (criterion 4), having participants with age range outside of 18-24 years (criterion 1), and for not including driver performance as dependent variables (criterion 5). The 10 remaining papers were included in the systematic review.

Table 3.3 illustrates the search statement terms and limiters, and the number of papers initially identified for inclusion in the review. Figure 3.1 presents the data extraction flowchart.

Table 3.3 Search statements and limiters

No	Database	Primary Search Dates	Search Statement/limiters	Search results	Primary selected results	Results selected for review	Update search date	Update search results	Selected results from update search	Total selected papers
1	Transportation research Information Database	12/08/2014	Statement (a) Publication date from Jan/2004 to Aug/2014	132	111	56	7/12/2014	3	3	59
2	PsycINFO (via EBSCOhost)	27/07/2014	Statement (b) Published Date: 20140108-20141231; Scholarly (Peer Reviewed) Journals; Age Groups: Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older)	69	56	48	8/12/2014	6	5	53
3	PsycARTICLES (via EBSCOhost)	27/07/2014	Statement (b) Published Date: 20040101-20140731; Scholarly (Peer Reviewed) Journals; Age Groups: Adulthood (18 yrs & older), Young Adulthood (18-29 yrs), Thirties (30-39 yrs), Middle Age (40-64 yrs), Aged (65 yrs & older), Very Old (85 yrs & older)	80	0	0	8/12/2014	0	0	0

No	Database	Primary Search Dates	Search Statement/limiters	Search results	Primary selected results	Results selected for review	Update search date	Update search results	Selected results from update search	Total selected papers
4	MEDLINE (via EBSCOhost)	27/07/2014	Statement (b) Date of Publication: 20040101-20140731; Human; Age Related: Young Adult: 19-24 years, Adult: 19-44 years, Middle Aged: 45-64 years, Middle Aged + Aged: 45 + years, Aged: 65+ years, Aged, 80 and over, All Adult: 19+ years	84	56	45	9/12/2014	0	0	45
5	ScienceDirect	27/07/2014	Statement (b) In Psychology, Neurosciences and social sciences From 2004 to present (27/07/2014)	87	37	22	9/11/14	11	0	22
6	ProQuest Psychology journals database	01/08/2014	Statement (b) Date: From 01 January 2004 to 31 July 2014 Age group: Adult (19-44 years), Aged (65+ years), Aged (80+ years), Middle aged (45-64 years) Source type: Books, Dissertations & Theses, Scholarly Journals.	138	17	2	9/12/14	0	0	2
7	Web of Science	6/08/2014	Statement (b) Date from 2004 to date	16	10	6	9/12/14	22	4	10

No	Database	Primary Search Dates	Search Statement/limiters	Search results	Primary selected results	Results selected for review	Update search date	Update search results	Selected results from update search	Total selected papers
8	Scopus	8/08/2014	Statement (b) Date from 2004 to date	215	169	81	12/12/2014	8	2	83
9	Ergonomic Abstacts (via EBSCOhost	8/08/2014	Statement (b) using smart search Publication date from Jan 204 to Aug2014	30	20	13	14/12/2014	4	4	17
10	PubMed in NCBI	8/08/2014	Statement (b) in NBCI homepage Additional filters: publication date from 1/01/2004 to 31/08/2014, Age 19+ years	84	52	24	14/12/2014	0	0	24
11	The Cochrane library	11/08/2014	Statement (a) Publication date from Jan/2004 to Aug/2014	7	1	0	14/12/2014	0	0	1
12	Trip database	11/08/2014	Statement (b) From:2004 to:2014	1134	23	10	14/12/2014	0	0	10

No	Database	Primary Search Dates	Search Statement/limiters	Search results	Primary selected results	Results selected for review	Update search date	Update search results	Selected results from update search	Total selected papers
13	EMBASE	11/08/2014	Statement (a) Publication date from 2004 to 2014	196	61	39	14/12/2014	6	3	42
14	CINAHAL (via EBSCOhost)	12/08/2014	Statement (b) Published Date: 20040101-20140831; Peer Reviewed; Human; Age Groups: Adult: 19-44 years, Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over	59	9	1	14/12/2014	0	0	1

Search statements: (driver or simulator or vehicle or "commercial driver" or "Professional driver" or "driver performance" or "truck driver" or "bus driver") and (sleepiness or drowsiness or hypersomnolence or "sleep onset" or "excessive sleepiness" or "sleep propensity" or fatigue or microsleep or alertness or vigilance or hypovigilance) and ("sleep deprivation" or "sleep loss" or "sleep limitation" or "sleep restriction")

("sleep depriv*" OR "sleep loss" OR "sleep limitation" Or "sleep restriction") AND TX ("sleepiness" OR drows* OR hypersomnol* OR "sleep onset" OR "excessive sleep*" OR "sleep propensity" OR fatigue* OR microsleep* OR alert* OR vigilance OR hypovigilan*) AND TX (driver OR simulator OR vehicle OR "commercial drivers" OR "professional driver" OR "driver performance" OR " truck driver" OR "bus driver")

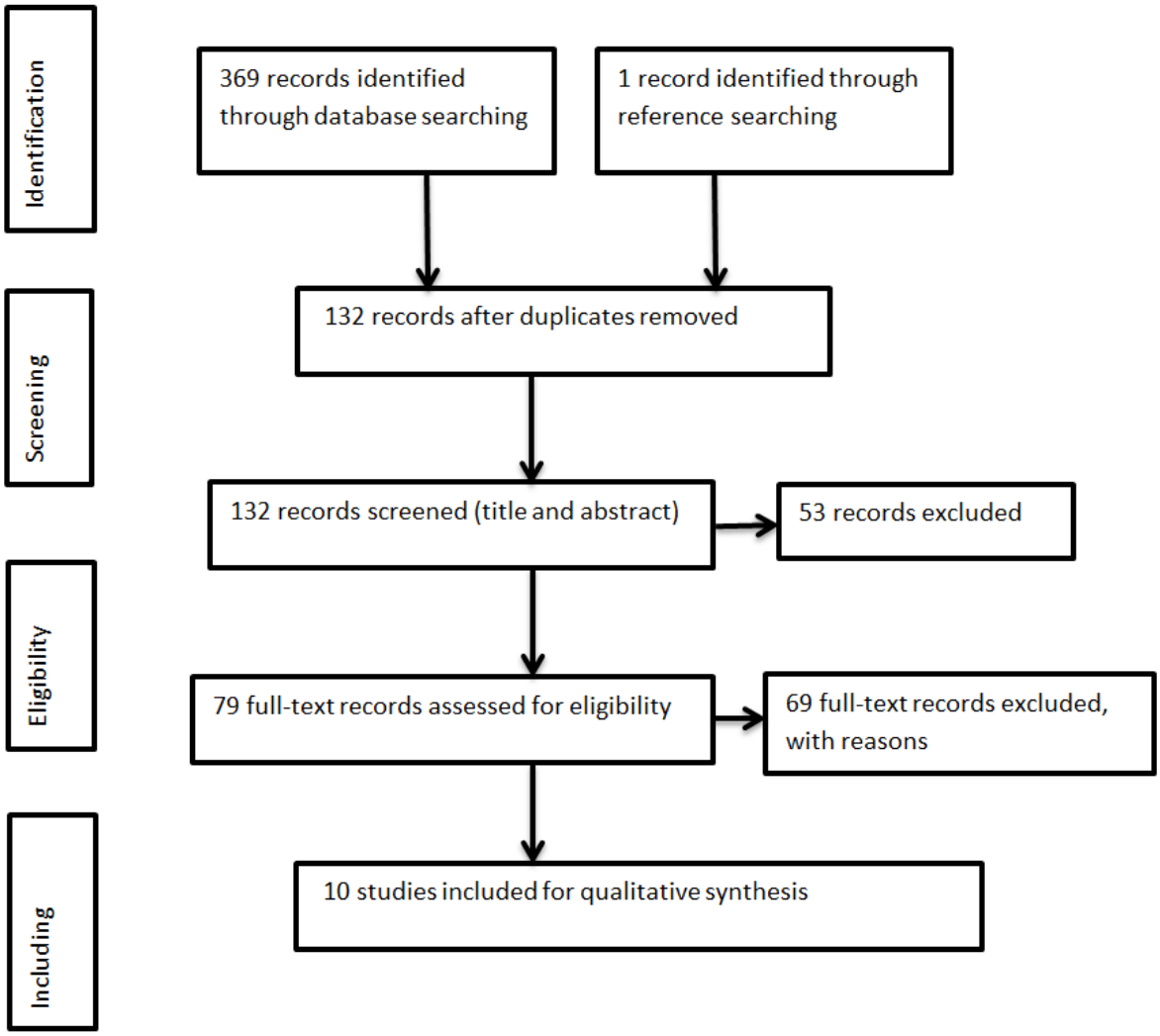

Figure 3.1. Data extraction flowchart based on the PRISMA statement

3.4.2 **Summary of reviewed papers**

Study design and sample size

There was no available randomised control trial within the body of evidence. Instead, there was a homogenous group of quasi-experimental studies including cross-over (n = 3), between-groups (n = 4) and within-group (n = 3) designs. All papers reported on more than one outcome measure. The sample sizes ranged from 8 to 41 participants, with less than 15 subjects for five papers, between 20 to 26 subjects for three papers and 40 to 41 participants for two papers. Most studies recruited only male participants, with only three reports including female participants (Contardi, Pizza, Sancisi, Mondini, & Cirignotta, 2004; Lowden et al., 2009; Pizza, Contardi, Mostacci, Mondini, & Cirignotta, 2004; Rupp, Arnedt, Acebo, & Carskadon, 2004). The study designs, sample sizes, and age ranges of participants are presented in Table 3.4. Table 3.5 provides sleep deprivation regimes in the reviewed papers and Table 3.6 shows the driving settings across the reviewed studies.

The driving tasks differed in terms of time of driving, coincidence with sleep deprivation time, the frequency of driving, and the duration of the drives. For instance, driving time (time-on-task) ranged from 10 min to 8 hours, with five studies examining durations of 1.5 to 2 hours, and four studies using short drives of either 30 minutes or 10 minutes. Only one study adopted a long driving protocol of 4 and 8 hours. These significant differences in sample size, the sleep deprivation paradigms and driving tasks presented challenges for comparing the findings and for assessing the generalisability of the findings.

Table 3.4 Study designs, sample sizes and age range of participants in the reviewed papers

Study design	Sample size and age range		
	N < 16	20 < N < 27	39 < N < 42
Cross over	(Philip et al., 2005$_{(b)}$) (12 men; 19-24 yrs.), (14 men; 21–25 yrs.)	(Philip et al., 2005$_{(a)}$) (22 men; 18-24 yrs.),	
Between-groups		(Lowden et al., 2009) (5 young men, 5 young women; 18–24 yrs.), (5 old men, 5 old women; 55–64 yrs.)	(Matthews et al., 2012$_{(b)}$) (41 men: mean 21.8 (± 3.8) yrs.), (Filtness, Reyner, & Horne, 2012) (20 young men; 20–26 yrs., 20 old men; 52–74 yrs.)
Within-groups	(Anderson & Horne, 2013) (8 men; 20-26 yrs.), (Matthews et al., 2012$_{(a)}$) (14 men; mean 21.8 (± 3.8) yrs.)		
Not reported explicitly	(Pizza et al., 2004) (10 men, 10 women; mean 24.9 (± 0.6) yrs.)	(Rupp et al., 2004) (13 men, 13 women; 18- 26 yrs.)	

Table 3.5 Sleep deprivation regimes in the reviewed papers

Driving setting	Duration	Acute sleep loss			Chronic sleep loss	Extended wake
		Moderate	Severe	Total	Moderate to severe	
Simulator	10 min				(Matthews et al., 2012$_{(a)}$), (Matthews et al., 2012$_{(b)}$)	
	30 min	(Rupp et al., 2004)	(Rupp et al., 2004)	(Pizza et al., 2004)		
	1.5 hours					(Lowden et al., 2009),
	2 hours					(Anderson & Horne, 2013), (Filtness et al., 2012)
On-road	4 hours					(Sagaspe, P et al., 2008), (Verster, Taillard, Sagaspe, Olivier, & Philip, 2011)
	8 hours					(Sagaspe, P et al., 2008),(Verster et al., 2011)
Simulator/ on-road	1.5 hours		(Philip et al., 2005$_{(a);}$ Philip et al., 2005$_{(b)}$)			

Table 3.6 Driving setting in the reviewed papers

Author	Type of driving setting
*(Sagaspe, P et al., 2008), (Verster et al., 2011)	Two- lane highway
(Anderson & Horne, 2013)	Immobile car with a computer generated road projection
(Philip et al., $2005_{(b)}$)	Divided Attention Steering Simulator (Stowood Scientific Instruments, Oxford, UK)
*(Pizza et al., 2004), (Contardi et al., 2004)	STISIM 300 Driving Simulator, System Technology Incorporated, Hawthorne, USA
(Matthews et al., $2012_{(a)}$)	York Driving Simulator (YDS; DriveSim 3.00; York Computer Technologies, Kingstone, Ontario, Canada
(Matthews et al., $2012_{(b)}$)	York Driving Simulator (YDS; DriveSim 3.00; York Computer Technologies, Kingstone, Ontario, Canada
(Philip et al., $2005_{(a)}$)	Open Highway
(Lowden et al., 2009)	Hi-Fi moving base simulator (Volvo 850, Volvo Personbilar Sweden AB, Gothenburg, Sweden)
(Filtness et al., 2012)	Immobile car with a computer generated road projection

*One study published in two papers

3.4.3 **Magnitudes of effects (effect sizes)**

Table 3.7 provides a summary of the magnitude of findings arranged by outcome measures. Of the 10 papers reviewed in this study, nine lacked any report of effect sizes such as partial eta square, Cohen's d, coefficient of correlation (r), or coefficient of determination (r^2) in their results. Only one paper (Rupp et al., 2004), reported the effect sizes as Cohen's d. Most studies reported unstandardized effect sizes (the differences in outcome variables reported in the actual units of that variable), and some of them reported their results as confidence intervals.

Table 3.7 Summary of reviewed papers and magnitudes of effects

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
Lateral position	(Philip et al., $2005_{(b)}$), France	Car distance from lateral lanes, Cross-over study comparing 6 times real and simulated driving after habitual sleep (8 h) or only sleep for 2 hours, from 11p.m. to 1 a.m.)	Sleep for 2 h, from 11p.m. to 1 a.m.)	1.5 h	6 times/ day from 9 a.m. to 9:30 p.m.	This variable was not a primary interest outcome, but was prerequisite of other outcomes.
	(Philip et al., $2005_{(a)}$), France	Car distance from lateral lanes, Cross-over study comparing 5 times real driving after habitual sleep (8 h) or only sleep for 2 hours, from 11 p.m. to 1 a.m.)	Sleep for 2 hours, from 11 p.m. to 1 a.m.)	1.5 h	5 times/ day from 9 a.m. to 7:30 p.m.	This variable was not a primary interest outcome, but was prerequisite of other outcomes.
	(Matthews et al., $2012_{(b)}$), Australia	Distance from centre of the car to the left lane marker, Between-participant comparison, comparison of control group and medium and severe sleep deprived groups	Chronic sleep loss in two doses: 1 h sleep loss, and 3 h sleep loss	10 min	8-9 times/day, Both day and night time, Rotating sleep/wake in to forced desynchrony	This variable was not a primary interest outcome, but was prerequisite of other outcomes.
	(Matthews et al., $2012_{(a)}$), Australia	Distance from centre of the car to the left lane marker, Within-participant comparison of each participant after normal sleep with chronic moderate sleep	Chronic sleep loss, 3 h sleep loss (5 h sleep)	10 min	9 times/day, Both day and night time, Rotating sleep/wake in	No effect of day (sleep debt) on mean lane position

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		deprivation by 7 periods of forced desynchronized with 23.33 h of wake followed by 4.67 h of time in bed			to forced desynchrony	
	(Pizza et al., 2004), Italy	Distance from the car to the left lane marker, within-participant comparison of each participant after normal sleep with after sleep deprivation	Total sleep loss for one night	30 min	4 times/day between morning and afternoon	This variable was not a primary interest outcome, but was prerequisite of other outcomes.
	(Lowden et al., 2009), Sweden	Perpendicular distance between the right side of the right front wheel and the left side of the right-hand lane boarder, between-participant comparison of performance of young and elderly participant after normal sleep with extended wakefulness	5.5 h sleep loss (extended wake) and 2 h sleep	1.5 h	Dual drives in afternoon and night time	This variable was not a primary interest outcome, but was prerequisite of other outcomes.
	(Philip et al., $2005_{(b)}$), France	Mean lateral deviation from centre of the road, Cross-over study comparing 6 times real and simulated driving after habitual sleep (8 h) or only sleep for 2 hours, from 11 p.m. to 1 a.m.)	Sleep for 2 h, from 11 p.m. to 1 a.m.)	1.5 h	6 times/ day from 9 a.m. to 9:30 p.m.	This variable was not a primary interest outcome, but was prerequisite of other outcomes.
	(Pizza et al., 2004), Italy	Deviation in road position from lane centre,	Total sleep loss for one	30 min	Between morning and	Mean lane position did not show any significant difference in the different simulation sessions ($\chi 2$ =

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		Within-participant comparison of each participant after normal sleep with after sleep deprivation	night		afternoon	0.99)
	(Rupp et al., 2004), Brown University	Moderate Sleep loss (5 h sleep) for restricted group (n = 13), Severe Sleep loss (3 h sleep) for restricted group (n = 13)	Sleep loss for 3 h, Sleep for 5 hours	30 min	between 1a.m and 9 a.m., between 3 a.m. and 9 a.m.	No significant main effects or interactions were found for Lane deviation (F = 0.3)
SD of lateral position	(Pizza et al., 2004), Italy	Lateral position: distance from the car to the midline, Within-participant comparison of each participant after normal sleep with after sleep deprivation	Total sleep loss for one night	30 min	Between morning and afternoon	The lane position variability had a significant increase with the highest increase of 0.20 from basal condition (0.32) to sleep deprived condition (0.52) at 2 p.m. ($\chi 2 = 0.003$, $p<0.05$). Effects size has not been reported.
	(Matthews et al., $2012_{(b)}$), Australia	Lateral position: distance from centre of the car to the left lane marker. Between-participant comparison, comparison of control group and medium and severe sleep deprived groups	Chronic sleep loss, 1 h sleep loss (7 h sleep), 3 h sleep loss (5 h sleep)	10 min	8-9 times/day Both day and night time, Rotating sleep/wake due to forced desynchrony	Sleep dose of either moderate or severe sleep restriction significantly increased SD of lateral position ($F_{2,1923} = 95.81$, $p < 0.001$). Significant effect of chronic sleep debt (day) only in moderate sleep restriction ($F_{6,1923} = 7.96$, $p < 0.001$); The standard deviation of lateral position increased from -0.02 m on day 1 to -0.05 m on day 7. A significant effect of times of day ($F_{5,1923} = 17.96$, $p < 0.001$); in moderately sleep restricted group SD of lateral position increased from -0.0.75 m at 180° after nadir to 0.025 at 60° after nadir, a rise of 0.1 m.

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
						A significant effect of prior wake ($F_{8,1923} = 4.33$, $p < 0.001$); moderate sleep restriction SD of lateral position increase from -0.075 m after 2 hours of prior wake to 0.05 m after 20 hours of prior wake, an increase of 0.125 m
	(Lowden et al., 2009), Sweden	Lateral position: perpendicular distance between the right side of the right front wheel and the left side of the right-hand lane boarder, Between-participant comparison of performance of young and elderly participant after normal sleep with extended wakefulness	5.5 h sleep loss (extended wakefulness) and 2 h sleep	1.5 h	Dual drives in afternoon and night time	From 30th minutes of drive onwards the standard deviation of lateral position increased from 0.17 in the early evening drive to 0.3 in the night time drive. Effects size has not been reported
	(Matthews et al., 2012$_{(a)}$), Australia	Lateral position: distance from centre of the car to the left lane marker, Within-participant comparison of each participant after normal sleep with chronic moderate sleep deprivation by 7 forced desynchronized periods of 23.33 h of wake followed by 4.67 h of time in bed	Sleep loss for 3 hours, Sleep for 5 hours	10 min	Midnight	The standard deviation of lane position (m) after sleep loss was significantly higher at different times of day ($p < 0.001$) or various prior wake times ($p = 0.005$) or different days with growing sleep debt ($p = 0.008$), with the highest difference of 0.065 m and 0.05 m at 60° after nadir and after 22 hours of prior wake respectively. Effects size has not been reported
	(Rupp et al., 2004), Brown	Lateral position: deviation from centre of the road,	Sleep loss for 3 h,	30 min	between 1a.m. and 9 a.m.,	A significant interaction of group and task type: lane variability was greater among sleep deprived

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
	University	Between-group comparison group after normal sleep, moderate and severe Sleep deprivation	Sleep for 5 h		between 3 a.m. and 9 a.m.	group for the dual driving and subtraction task versus the single driving task **(**medium effect size, Cohen's d = 0.79), A significant interaction of group and session: lane variability was greater among sleep deprived group than the control group, Cohen's d = 0.85 (large effect size)
Inappropriate line crossing (ILC)	(Sagaspe, P et al., 2008), France	Inappropriate line crossing (ILC) car crosses one of lateral lane markers, Cross-over design comparison of each participant the effect of 2, 4 and 8 h night time driving (extended wakefulness) on every participant	Sleep loss for 6 h (extended wake), Sleep for 2 h	2 h, 4 h, 8 h	Midnight at the wake time	Compared to the reference session (9–10 p.m.), the incidence rate ratios of inappropriate line crossings were 6.0 (95% CI, 2.3 to 15.5; P,.001), 15.4 (CI, 4.6 to 51.5; P,.001) and 24.3 (CI, 7.4 to 79.5; P,.001), respectively, for the three different durations of driving, Effects size has not been reported
	(Anderson & Horne, 2013), UK	Driving incidents characterise d by at least two wheels of the vehicle leaving the carriageway, Within-participant comparison of each participant after normal sleep with extended wakefulness	Sleep loss for 3 h, Sleep for 5 h	2 h	Afternoon at 2 p.m.	There was a positive correlation between number of distractions and number of lane crossings under sleep restriction (large effect size r = 0.74), such that from 2308 distractions under sleep deprivation 474 distraction directly resulted in incidents (t = 2.73; df = 7; p < 0.03).
	(Matthews et al., 2012$_{(a)}$), Australia	Lane violation (crash): centre of the car leaves the road or car hits the adjacent car, Within-participant comparison of each participant after normal sleep	Sleep loss for 3 h, Sleep for 5 h	10 min	Midnight	The number of line crossings (lane violations), after sleep loss was significantly higher at different times of day (p < 0.001) or various prior wake times (p < 0.001) or different days of experiment (p < 0.001), compared to baseline results, with the highest

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		with chronic moderate sleep deprivation by 7 periods of forced desynchronized with 23.33 h of wake followed by 4.67 h of time in bed				difference of 0.32 count and 0.30 count at 60° after nadir and after 22 hours of prior wake respectively. Effects size has not been reported
	(Philip et al., $2005_{(b)}$), France	Line crossings: car crosses one of lane markers, Cross-over study comparing 6 times real and simulated driving after habitual sleep (8 h) or only sleep for 2 hours, from 11 p.m. to 1 a.m.)	Sleep loss for 7 h, Sleep for 2 h	1.5 h for 5 times	morning	Not reported explicitly, a significant main effect of sleep deprivation on inappropriate line crossings ($F_{1,10} = 60.013$, $P < .001$) increase from 50 in rested condition to 190 times in sleep- deprived condition, a significant increase of 8 times from zero in rested condition to 8 in sleep-deprived condition, Time of day in this study had no main effect on lane crossing ($F_{5,50} = 1.274$, $P = 0.301$), Effects size has not been reported
	(Philip et al., $2005_{(a)}$), France	Line crossings: car crosses one of lane markers, Cross-over study comparing 5 times real driving after habitual sleep (8 h) or only sleep for 2 hours, from 11 p.m. to 1 a.m.)	Sleep loss for 7 h, Sleep for 2 h	1.5 h	daytime	Total crossings increased after sleep restriction (535 crossings in the sleep-restricted condition versus 66 after non-restricted sleep (incidence rate ratio (IRR): 8.1(95% CI): 3.2–20.5; $p < 0.001$)), from the first driving session, Effects size has not been reported
	(Rupp et al., 2004), Brown University	Line crossings: car crosses one of lane markers, Between-group comparison group after normal sleep, moderate and	Sleep loss for 3 h, Sleep for 5 h	30 min	A time between midnight and morning	Mean lane crossing increase by 1.4 (from 2.1 after normal sleep to 3.5 after sleep loss) for single driving task and by 1.6 (from 2.4 after normal sleep to 4 after sleep loss) on dual driving and subtracting

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		severe sleep deprivation				task. This study reported a significant interaction of sleep condition (rested vs restricted) and experimental session on lane crossing (large effect size; Cohen's d = 0.98).
	(Filtness et al., 2012), UK	All four wheels came out of the driving lane (lane departure), Repeated measures between-group design comparing two conditions of a normal prior night's sleep and sleep restricted to 5 h (extended wakefulness among young and elderly drivers	Sleep loss for 3 h (extended wake, sleep for 5 h)	1.5 h	afternoon	A significant condition by group interaction showed an increase in incidence of lane crossing in the last 30 minutes of a 1.5 h drive in both young and old drivers [$F_{1,38}$ =27.67, p = 0.000, ε = 1], the number of incidents in old drivers rose from zero to 2 while young drivers were more impaired [$F_{1,38}$ = 9.92, p = 0.003, ε = 1] with increase of incidents from 4 to 8. Effects size has not been reported.
	(Pizza et al., 2004), Italy	Number of crashes: it is not defined in the paper Within-participant comparison of each participant after normal sleep with after sleep deprivation	Total sleep loss for one night	30 min	Between morning and afternoon	The number of crashes had a significant increase with the highest increase of 0.8 from basal condition (0.00) to sleep deprived condition (0.8) at 2 p.m. Effects size has not been reported
Mean and SD of speed	(Pizza et al., 2004), Italy	Within-participant comparison of each participant after normal sleep with after sleep deprivation	Total sleep loss for one night	30 min	Between morning and afternoon	No significant, worsening of mean speed ($\chi2$ = 0.98, p > 0.05) and the standard deviation of speed ($\chi2$ = 0.21, p > 0.05) after sleep deprivation.
	(Lowden et al., 2009), Sweden	Between-participant comparison of performance of young and elderly participant after normal sleep with	5.5 h sleep loss (extended	1.5 h	Dual drives in afternoon and night time	Not reported

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		extended wakefulness	wake; 2 h sleep)			
	(Matthews et al., 2012$_{(a)}$), Australia	Within-participant comparison of each participant after normal sleep with chronic moderate sleep deprivation by 7 forced desynchronized periods of 23.33 h of wake followed by 4.67 h of time in bed	Sleep loss for 3 h, Sleep for 5 h	10 min	Midnight	Mean speed ($p = 0.016$) were both different after sleep deprivation over different days. The standard deviation of speed (km/h) after sleep loss was significantly higher at different times of day ($p < 0.006$), and on different days ($p = 0.010$), but not at various prior wake times ($p > 0.05$). The highest difference of 0.55 km/h in the standard deviation of speed was recorded at 60° after nadir under sleep deprivation. Effect of day has not been reported
Deviation from the speed limit	(Contardi et al., 2004), Italy	Frequency of exceeding the speed limit 120km/h, Within-participant comparison of each participant after normal sleep with after sleep deprivation	Total sleep loss for one night	30 min	Between morning and afternoon	A significant change from 3.8 to 10.5 during daytime drive, an increase of 6.7 ($\chi 2 = 0.018$, $p < 0.05$). Effects size has not been reported
	(Matthews et al., 2012$_{(a)}$), Australia	Mean deviation from speed limit (80 and (80 and 100 km/h), Within-participant comparison of each participant after normal sleep with chronic moderate sleep deprivation by 7 forced desynchronized periods of 23.33 h of wake	Sleep loss for 3 h, Sleep for 5 h	10 min	Midnight	The 'Day' variable, capturing the growing sleep debt through the protocol, had also significant effect. The magnitude of effect was not reported.

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		followed by 4.67 h of time in bed				
	(Rupp et al., 2004), Brown University	Between-group comparison group after normal sleep, moderate and severe Sleep deprivation	Sleep loss for 3 h, Sleep for 5 h	30 min	A time between midnight and morning	No effect on mean deviation from speed limit (F = 0.58, P > 0.05)
Speed variability	(Matthews et al., 2012$_{(a)}$) Australia	SD of deviation from speed limit (80 and (80 and 100 km/h), (speed variability), Within-participant comparison of each participant after normal sleep with chronic moderate sleep deprivation by 7 forced desynchronized periods of 23.33 h of wake followed by 4.67 h of time in bed.	Sleep loss for 3 h, Sleep for 5 h	10 min	Midnight	Not reported explicitly, according to the figure speed variability increased from -0. 1 at circadian 180 degrees after nadir to 0.55 at circadian phase 60 degree, Effects size was not reported
	(Rupp et al., 2004), Brown University	Between-group comparison group after normal sleep, moderate and severe Sleep deprivation.	Sleep loss for 3 h, sleep for 5 h	30 min	A time between midnight and morning	No effect on the standard deviation of deviation from speed limit (F = 3.47, P > 0.05)
Speed violation	(Matthews et al., 2012$_{(a)}$), Australia	Speed violation: cumulative time that speed was 5 km/h more than speed limit (80 and 100 km/h), Within-participant comparison of each participant after normal sleep	Sleep loss for 3 h, sleep for 5 h	10 min	Midnight	The 'Day' variable, capturing the growing sleep debt through the protocol, had also significant effect. The magnitude of effect has not been reported. Effects size has not been reported

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
		with chronic moderate sleep deprivation by 7 forced desynchronized periods of 23.33 h of wake followed by 4.67 h of time in bed.				
Reaction time	(Pizza et al., 2004), Italy	Mean reaction time from divided attention test on the simulator, Within-participant comparison of each participant after normal sleep with after sleep deprivation.	Total sleep loss for one night	30 min	Between morning and afternoon	The mean reaction time had a significant increase with the highest increase of 0.58 s from basal condition (1.34) to sleep deprived condition (1.92) at 2 pm, a rise of o.58 s ($\chi 2 = 0.004$, $p < 0.05$). Effects size has not been reported.
	(Philip et al., $2005_{(a)}$), France	Reaction time from PALM personal organizer, Cross-over study comparing 5 times real driving after habitual sleep (8 h) or only sleep for 2 hours, from 11 p.m. to 1 a.m.).	Sleep loss for 7 h, sleep for 2 h	1.5 h	daytime	A significant main effect for time of day and condition and the interaction between the two factors was observed ($F_{1,21} = 20.447$; $P < 0.001$). Effects size has not been reported.
Mean 10% slowest reaction time	(Philip et al., $2005_{(b)}$), France	10% slowest reaction time from visual task on the simulator, Cross-over study comparing 6 times real and simulated driving after habitual sleep (8 h) or only sleep for 2 hours, from 11 p.m. to 1 a.m.).	Sleep loss for 7 h, sleep for 2 h	1.5 h for five times	morning	The mean 10% slowest reaction time had a significant increase of 137 milliseconds during simulated driving (670 milliseconds vs 533 milliseconds), ($F_{1,11} = 13.083$, $p = 0.004$). The mean 10% slowest reaction time had a significant increase of 223 milliseconds after sleep deprivation (713 milliseconds vs 490 milliseconds), Effects size has not been reported.

Outcome	Author	Definition/analysis	Sleep deprivation	Drive time	Time of day	Outcome magnitude/effect size
Reaction time from dual driving and subtraction task	(Rupp et al., 2004), Brown University	Reaction time from subtraction task for 1 sec and dual driving and subtraction task, Between-group comparison group after normal sleep, moderate and severe Sleep deprivation.	Sleep loss for 3 h, sleep for 5 h	30 min	A time between midnight and morning	Main effect of task type on reaction time with longer reaction times on the dual task than on the single subtraction task (large effect size; Cohen's d = 1.51). .
Distraction	(Anderson & Horne, 2013), UK	Distraction: looking away from the main road way for >3 s, Within-participant comparison of each participant after normal sleep with extended wakefulness.	Sleep loss for 3 h, sleep for 5 h	2 h	Afternoon at 2 p.m.	Curtailed sleep on the night prior to an afternoon drive led to a fourfold increase in long distractions. Effects size has not been reported.

SD= standard deviation

Lane crossing

Inappropriate line crossing has been defined variously as crossing one lateral lane marker, running off the road at least by two wheels, and leaving the road by all four wheels.

Of the 10 studies, eight papers reported findings of lane crossing. In three studies (Philip et al., 2005$_{(a);}$ Philip et al., 2005$_{(b);}$ Sagaspe, P et al., 2008), drivers' sleep was severely restricted to only two hours sleep, and they drove for durations between 1.5 to 2 hours. In one study (Philip et al., 2005$_{(b)}$), sleep deprivation increased the total number of inappropriate line crossings in simulation by 140 events, from 50 cases in rested condition and up to 190 cases after sleep loss. The latter authors found considerably lower line crossing in on-road driving, but there was still a significant increase of 8 events in this variable after sleep deprivation when compared with no occurrence of line crossing in rested condition. In another study (Sagaspe, P et al., 2008), the number of inappropriate line crossings in the last hour of 3 nocturnal driving sessions were 6, 15, and 24-fold greater than those of the reference driving session (9–10 p.m.), respectively. In another study (Philip et al., 2005$_{(a)}$), after 6 hours sleep deprivation (2 hours sleep) and 10 hours (5 x 90 minutes) on-road driving, the cumulative number of inappropriate line crossing per person rose from 469 events from 66 cases in rested condition to 536 cases after sleep loss. The maximum increase of 120 events (8-fold) occurred in the last 1.5 hour driving session in the late afternoon, probably due to cumulative fatigue from long driving time.

In a study with moderate sleep loss of three hours (Filtness et al., 2012), sleep deprivation increased the incidence of lane crossing in the last 30 minutes of a 1.5 hour drive in both young and old drivers by 2 and 4 cases, respectively. In the study by Rupp et al. (2004), after a similar degree of sleep loss (3 hours), but during shorter drives of 30 minutes, sleep deprivation led to an increase of 1.4 in mean lane crossings for single driving task, and by 1.6 on dual driving and subtracting tasks.

Lateral position variables

Mean lateral position was not the primary outcome in most studies and was measured to determine other variables, mostly standard deviation of lateral position. Therefore

the effects of sleep loss on this variable was not reported except in two studies (Pizza et al., 2004), and (Rupp et al., 2004), with no effect of sleep loss on this outcome.

Variability in lane positioning, typically described by the standard deviation of lateral position in the reviewed studies, was defined as the distance from a certain point on the car (i.e. the centre of the car, right side of the right front wheel) to some reference point on the road (i.e. roadway midline, one of lane markers, left lane marker). Larger and more frequent deviations represented a higher risk of running off the road (line crossing) or hitting adjacent cars. The standard deviation of lateral position was reported in five of the reviewed papers (Lowden et al., 2009; Matthews et al., 2012$_{(a);}$ Matthews et al., 2012$_{(b);}$ Pizza et al., 2004; Rupp et al., 2004).

A 1.5-hour night time simulated driving during an extended wake from 5 and 7 hours (Lowden et al., 2009) could increase the standard deviation of lateral position by 1.2 after the 30th minute of driving compared to driving in the rested condition.

Total sleep loss in the study by Pizza et al. (2004) resulted in an increase of 0.20 in standard deviation of lateral position after a 30-min drive in daytime.

There was no main effect of sleep loss on the standard deviation of lateral position in the study by Rupp et al. (2004) after sleep loss of 3 to 5 hours.

An important point to consider is the interaction between sleep loss and the time of day (of either the loss or the subsequent testing). Matthews et al. in two studies with similar protocol but different doses of sleep loss (2012$_{(a);}$ 2012$_{(b)}$), enforced a 28-h day compared to usual 24-h circadian day for one week. A 3-hour sleep deprivation condition with short drive of 10 minutes occurring at 2.5 hour intervals after waking was included within this forced desynchrony protocol. After sleep loss the number of line crossings (lane violations) (Matthews et al., 2012$_{(a)}$) and the standard deviation of lane position were higher after either circadian nadir (early morning), after 22 hours of prior wake (Matthews et al., 2012$_{(a)}$).

Speed variables

A variety of speed variables were reported in three studies (Matthews et al., 2012$_{(a);}$ Pizza et al., 2004; Rupp et al., 2004). Mean speed and standard deviation of speed in the study of Pizza et al. (2004) had no significant change during a 30-minute drive

after one night total sleep loss. The frequency of speeding (during which the driver exceeded the speed limit) also showed a significant increase of 6.7 during daytime driving. However, no estimate of the effect sizes was reported. In the study of Rupp et al. (2004) neither mean deviation, nor the standard deviation from speed limit showed a significant change during a 30-minute drive after sleep loss of either 3 hours or 5 hours when compared to the rested group.

Cognitive performance

In the study by Philip et al. ($2005_{(a)}$), a 7-hour sleep loss resulted in a significant main effect for differences in reaction time. Similarly, these authors in another study (Philip et al., $2005_{(b)}$), found a significant main effect of sleep loss on mean 10% slowest reaction time, with an increase of 223 milliseconds in the mean 10% slowest reaction after one week chronic sleep loss.

In another study by Pizza et al. (2004) mean reaction time during a daytime drive showed a rise of 0.58 second after one night total sleep loss.

3.4.4 **Direction of effects**

The possibility of conducting a formal meta-analysis to statistically combine the quantitative results was explored. However, due to the lack of reported standardised effect sizes, as well as the insufficiency, inconsistency, and non-comparability of the unstandardized reported effects, it was impossible to combine the data and obtain a single pooled estimated effect size for each outcome. The only possible analysis was to determine and summarise the *direction* of effects of sleep loss on each outcome measure. This approach has been taken recently in other sleep-related systematic reviews (Thorpe et al., 2015).

The numbers of papers reporting outcome measures and direction of effect have been represented in Figure 3.2. Of the in-vehicle performance outcomes, lane crossing, standard deviation of lateral position, and mean reaction time were the three most-often reported outcomes. Lateral position was not reported in most studies, and was only monitored to obtain lane crossing or standard deviation of lateral position. The standard deviation of lateral position, line crossing, and distraction were each

consistently reported to be impaired by sleep loss, while there were inconsistencies in other findings such as mean reaction time and speed related variables.

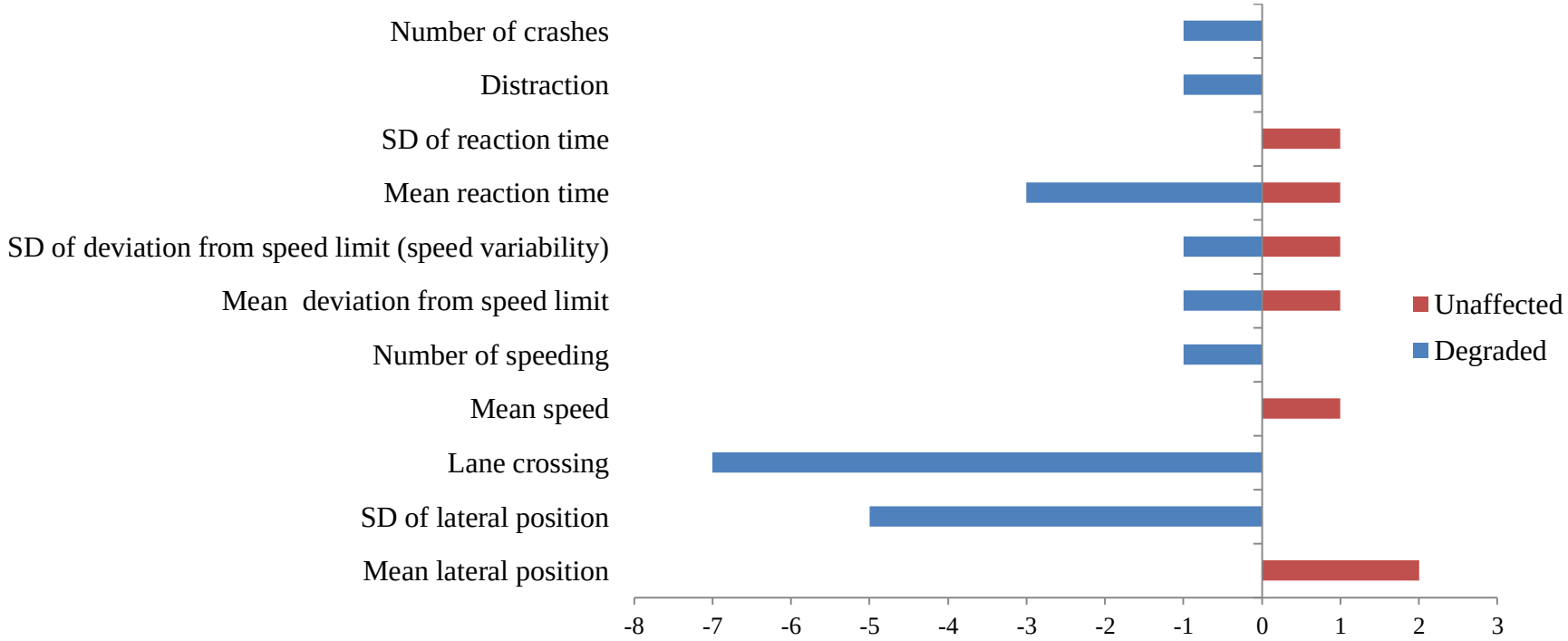

Figure 3.2. Direction of effects of sleep deprivation on outcome measures,

The X and Y axes reflect the number of papers and the outcome measures, respectively. These papers are not mutually exclusive.

3.4.5 **Methodological and reporting characteristics of studies**

In order to develop some GRADE criteria for rating the quality of individual papers, the methodological and reporting facets of the papers were closely investigated. It should be noted that some of these papers might be excellent in other ways, and the 'flaws' are about fitting to these criteria specifically. The methodological flaws and reporting faults of the papers, affecting the quality of findings, are presented in Table 3.8.

Some of important flaws were considered in the development of the GRADE criteria for quality grading. Within the 10 reviewed papers, the most common factor affecting the quality of papers was the lack of wake EEG measurements to confirm sleepiness of the participants during the driving tasks (eight papers did not measure wake EEG). Seven papers did not report their methods for controlling distraction sources as possible confounding factors. Methods of controlling for other confounders such as the consumption of caffeine, alcohol, or other stimulants/ sedatives prior to or during the experiments were not reported in five papers. Only two studies (Anderson & Horne, 2013; Filtness et al., 2012) monitored the effects of distraction (by split filming of the driver's face) and sleep deprivation (via Actigraphy beforehand, and by recording wake EEG during the experiment). Estimation of effect sizes were reported in only two studies as noted above, albeit not for all outcomes, and the remaining eight studies only reported unstandardized magnitudes of effects.

It is acknowledged that authors may actually have dealt with some of these methodological and reporting factors (e.g. a standardized lab environment). However, they have not explicitly reported them in the papers.

Table 3.8 Methodological elements of papers considered for quality rating

Paper	Methodological strengths and flaws	Factors considered for quality rating
(Philip et al., $2005_{(b)}$)	a. The reference point for measuring lateral position (centre or lateral side of the car etc.) was not reported, b. No measurement for possible distraction sources (confounders), c. No wake EEG measurement for confirming sleepiness, d. Not known if participants were professional drivers, shift workers, or had experienced recent time-zone travel, e. Consumption of caffeine, alcohol, and other stimulants/sedatives was not reported, f. Only males were included without any clear rationale for that, g. No criterion for quantifying driver experience (just yearly driving distance is given), h. Small sample size	a. No wake EEG measurement for confirming sleepiness, b. Small sample size
(Philip et al., $2005_{(a)}$)	a. The reference point for measuring lateral position (centre or lateral side of the car etc.) was not reported, b. No measurement for possible distraction sources (confounder), c. No wake EEG measurement for confirming sleepiness,	a. No wake EEG measurement for confirming sleepiness, b. Small sample size,

Paper	Methodological strengths and flaws	Factors considered for quality rating
	d. Not known if participants were professional drivers, shift workers, or had experienced recent time-zone travel, e. Consumption of caffeine, alcohol, and other stimulants/sedatives was not reported, f. Only males were included without any clear rationale for that, g. No criterion for quantifying driver experience (just yearly driving distance is given), h. Small sample size	
(Matthews et al., 2012$_{(b)}$)	a. Only males were included without any clear rationale for that, b. No measurement for possible distraction sources (confounder), c. No wake EEG measurement for confirming sleepiness, d. Consumption of caffeine, alcohol, and other stimulants/sedatives was not reported, e. No criterion for quantifying driver experience (just yearly driving distance is given), f. Large sample size, g. Presence of learning effect for lane deviation in the control condition,	a. No wake EEG measurement for confirming sleepiness, b. Big sample size, c. Presence of learning effect for lane deviation in the control condition,

Paper	Methodological strengths and flaws	Factors considered for quality rating
(Matthews et al., 2012$_{(a)}$)	a. Only males were included without any clear rationale for that, b. No measurement for possible distraction sources (confounder), c. No wake EEG measurement for confirming sleepiness, d. No criterion for quantifying driver experience (just yearly driving distance is given), e. Consumption of caffeine, alcohol, and other stimulants/sedatives was not reported, f. Small sample size,	a. No wake EEG measurement for confirming sleepiness, b. Small sample size
(Pizza et al., 2004)	a. The study design is not reported (within-participant design), b. The reference point (centre or lateral side of the car etc.,) has not been reported, c. Age range is not specified and method of control for age is unknown, d. No criterion for quantifying driver experience (just yearly driving distance is given), e. No measurement for possible distraction sources (confounder), f. No wake EEG measurement for confirming sleepiness, g. Small sample size,	a. No wake EEG measurement for confirming sleepiness, b. Small sample size

Paper	Methodological strengths and flaws	Factors considered for quality rating
(Lowden et al., 2009)	a. Small sample size, b. Good control for confounders, c. Wake EEG, EOG measurement for confirming sleepiness,	a. Small sample size, b. Good control for confounders, c. Wake EEG, EOG measurement for confirming sleepiness,
(Rupp et al., 2004)	a. The study design is not reported (between-participant design), b. No criterion for quantifying driver experience (just yearly driving distance is given), c. Good control for sleep deprivation, d. No wake EEG measurement for confirming sleepiness, e. No measurement for possible distraction sources (confounder),	a. Good control for sleep deprivation, b. No wake EEG measurement for confirming sleepiness,
(Sagaspe, P et al., 2008)	a. Type of lane crossing, partial (one wheel) or total (two wheel), was not reported, b. Good control for sleep deprivation before and during study, c. No wake EEG measurement for confirming sleepiness, d. No measurement for possible distraction sources (confounder), e. Results of the simulator might not be generalizable to real-life driving, except perhaps on a group level, f. Not known if participants were professional drivers, shift	a. Good control for sleep deprivation before and during study, b. No measurement for possible distraction sources (confounder), c. Results of the simulator may not be generalized to real-life driving, except perhaps on a group level, d. Small sample size

Paper	Methodological strengths and flaws	Factors considered for quality rating
	workers, or had experienced recent time-zone travel, g. Consumption of caffeine, alcohol, and other stimulants/sedatives was not reported, h. Only males were included without any clear rationale for that, i. Small sample size,	
(Anderson & Horne, 2013)	a. The side of the road to drive was not mentioned, b. The study design was not mentioned properly, c. Control for driver experience, d. Small sample size, e. Good control for distraction, f. Good control for sleep deprivation, g. No wake EEG for confirming sleepiness,	a. Small sample size, b. Good control for distraction, c. Good control for sleep deprivation,

Paper	Methodological strengths and flaws	Factors considered for quality rating
(Filtness et al., 2012)	a. Good sample size, b. Control for driving experience, c. The rationale for choosing only males was mentioned, d. Good control of driver sleep deprivation before and during test, e. Control for distraction by filming driver face, f. Wake EEG and EOG,	a. Good sample size, b. Good control of driver sleep deprivation before and during test, c. Control for distraction by filming driver face, d. Wake EEG and EOG,

3.4.6 **GRADE criteria**

In this systematic review some grading criteria were developed based on both the GRADE guidelines and the important flaws and strengths of the 10 reviewed papers. These criteria were utilized to downgrade and upgrade the quality of papers and are presented in Table 3.9. The study design criteria were adopted from the GRADE statement. Additionally, from the potential downgrading factors described in the GRADE statement (risk of bias, inconsistency, indirectness, imprecision, and publication bias) only "risk of bias" and "imprecision" criteria were adoptable, and from the upgrading factors only large effect size was applicable. From downgrading or upgrading factors specific to the reviewed papers, the factors listed in the column "factors considered for quality rating" in Table 3.8 were considered.

At the first stage of developing the grading criteria, the initial scores of 4, 2, 1 and 0 were first assigned to studies with RCT, longitudinal, quasi experimental and 'other' designs, respectively. Quasi-experimental designs that manipulated sleep and longitudinal studies that provided detail of the cumulative effects of chronic sleep deprivation have potential to show the magnitude and direction of effects of sleep loss on drivers' performance. Therefore, the GRADE scores were modified by adding 1 point to studies applying either of these two designs. As can be seen in Table 3.8, "risk of bias" was the major reason for decreasing the quality ratings for the papers, and this risk included inappropriate eligibility criteria, inadequate control for confounders, reporting bias, conflict of interest, and flaws in measuring sleepiness and outcome. Upgrading factors were categorised into three groups, including good control for exposure and inclusion criteria, some control for confounders, and increased precision (certainty) in statistical reporting. The presence of a downgrading factor led to deduction of one point from the initial rating attributed to the study, and each upgrading factor resulted in the addition of one point. The deduction of one point for every single downgrading factor would result in a negative quality score for a number of the studies, a status which has not been defined in GRADE (limited to a score of 0). Therefore, those factors with the *highest* impact on the quality of a given outcome were selected as follows:

a. From risk of bias: inadequate monitoring of sleepiness during test and practice effect.

b. From imprecision: not generalizable findings and small sample size.

c. From control for exposure and inclusion criteria: Strong control of sleep loss before test.

d. From certainty: large effect size, large sample size, objectively confirming sleepiness by EEG (for simulated drives) and control for distraction by filming the driver's face (for on-road drives).

Table 3.9 GRADE criteria and the criteria developed for grading the quality of papers for each outcome

Design quality	Quality score for design	Downgrading factors (1 score deducted)		Upgrading factors (1 score added)
High	**RTCs**, score 4	**Risk of bias:** Inappropriate eligibility criteria	Includes people with: Shift-work., professional driving, travel to different time zone in the last three months, Sleep disorders, Smoking, Habitual heavy caffeine consumption, Caffeine avoidance, Alcohol abuse (more than two standard drinks per day), Inclusion of people from a specific place only (e.g. university students only)	**Control for exposure and inclusion criteria:** Strong control of sleep loss before test, Strong inclusion criteria, **Confounders:** Residual confounders decreasing the estimated effect size, Strong control for confounders, **Certainty:** Large effect size, Large sample size, Confirming sleepiness with wake EEG, Control for distraction,

Design quality	Quality score for design	Downgrading factors (1 score deducted)		Upgrading factors (1 score added)
Low	**Observational study:** Experimental or longitudinal, score 3 Quasi-experimental or cross-sectional study, score 2 Other designs, score 0	Inadequate control for confounders	Age, Gender, Driving experience, Inter-individual differences in sensitivity to sleep loss,	
		Reporting bias	Unreported results for the outcome measures,	
		Conflict of interest	Study being funded by an organisation or industry increasing risk of reporting bias,	
		Flaws in measuring sleepiness and outcome	Inadequate monitoring sleep-wake before test, Inadequate control for stimulants before (sleep-wake monitoring time) and during	

Design quality	Quality score for design	Downgrading factors (1 score deducted)		Upgrading factors (1 score added)
			test,	
			Inadequate monitoring of sleepiness during test (no wake EEG)	
			Practice effect	
			Unclear definition of outcome	
			Inappropriate measurement of the outcome,	
		Imprecision (Uncertainty)	Small sample size affecting generalisability	
			Not generalizable findings	

3.4.7 **Quality of outcomes for individual papers and across the body of evidence**

The distribution of GRADE criteria and various downgrading and upgrading factors are provided in Table 3.10. Downgrading factors and upgrading factors are highlighted by yellow and green colours, respectively.

Based on these criteria, an Overall GRADE Score (OGS) was calculated for a given outcome in an individual paper. For instance, in Paper code 7, overall GRADE score for lateral position was calculated as:

OGS = (Quasi- experiment) + (Inadequate monitoring of sleepiness during test) + Large sample size

OGS = +2 - 1 + 1 = 2

As can be seen from Table 3.10, any individual paper could be assigned different quality scores for different outcome measures.

The last column of Table 3.10 represents the OGS for the body of evidence (that is, across all of the papers using the same outcome measure). To calculate the OGS, the magnitude of the contribution of each paper towards the quality of the body of evidence was taken into account. In the GRADE statement, papers with large sample sizes or more 'events' have a larger impact on the quality of evidence. However, there are no formal guidelines on how to include these two contributors in the quality context. The number of 'events' was not applicable in this review. There was no precedent for including the effect of sample size on the overall quality of the body of evidence. Therefore, a novel algorithm was developed for this literature as follows:

Overall Grade Score for the body of evidence (OGS) =

$$\frac{\sum(GRADE\ score\ for\ paper * Sample\ size\ of\ paper)}{Total\ sample\ size\ of\ the\ body\ of\ evidence}$$

OGSs < 1.5 were approximated to 1,

1.5 < OGSs < 2.5 were approximated to 2,

2.5 < OGS < 3 were approximated to 3.

For example, to calculate the OGS for lateral position, the sample sizes for all relevant papers were extracted from Table 3.4.

Using the above-mentioned algorithm, the OGS was calculated as follows:

OGS = (Zuzewicz et al.)/ (12 + 22 + 41 + 14 + 20 + 20) = 1.10 ~ 1

This GRADE rating is less than 1.5, and was therefore approximated to 1.

Table 3.10 Distribution of GRADE criteria and downgrading and upgrading factors of quality of outcomes for individual papers

		Downgrading factors for study design, risk of bias (limitations in execution) and imprecision														Upgrading factors					Overall GRADE Score	
		Study design			Risk of bias for other limitations				Risk of bias for flaws in measuring exposure(sleepiness) and outcome					Imprecision		Control for exposure and inclusion criteria (+1)	Confounder (+1)	Certainty (+1)			Overall GRADE score for each paper	Overall GRADE score for body of evidence
Outcome	Authors/ Code	RTC (+4)	Longitudinal (+3)	Quasi- experiment (+2)	Inappropriate /unclear eligibility criteria	Inappropriate /unclear control for confounders	Reporting bias	Conflict of interest	Inadequate monitoring sleep-wake	Inappropriate /unclear control for stimulants before and during test	Inadequate monitoring sleepiness during test (EEG)	Practice effect	Unclear definition of outcome	Findings not generalizable	Small sample size	Strong control of sleep loss before test	Strong inclusion criteria	residual confounding decreasing the estimated effect	Strong control for confounders	Large effect size	Large sample size	Objectively confirming sleepiness (PTC)	Control for distraction		
lateral position	(Philip et al., $2005_{(b)}$)			*	*	*	*				*		*		*			*					0	1
	(Philip et al., $2005_{(a)}$)			*	*	*	*	*			*		*		*			*					0	
	(Matthews et al., $2012_{(b)}$)			*		*	*	*			*							*			*		2	

Outcome	Authors/ Code	Downgrading factors for study design, risk of bias (limitations in execution) and imprecision										Upgrading factors			Overall GRADE Score	
	(Matthews et al., 2012(a))	*		*		*	*			*		*			0	
	(Pizza et al., 2004)	*		*	*		*		*	*		*			0	
	(Lowden et al., 2009)	*			*	*				*			*	*	3	
Mean lateral deviation from centre of the road	(Philip et al., 2005(b))	*	*	*	*					*		*			0	1.4
							*		*							
	(Pizza et al., 2004)	*		*			*		*	*		*			0	
	(Rupp et al., 2004)	*		*			*				*	*			2	
SD of lateral position	(Philip et al., 2005(b))	*	*	*	*					*		*			0	1.5
							*		*							
	(Pizza et al., 2004)	*		*			*		*	*		*			0	
	(Matthews et al., 2012(b))	*		*		*	*	*				*		*	1	
	(Lowden et al., 2009)	*				*				*			*	*	3	
	(Matthews et al., 2012(a))	*		*		*	*			*		*			0	

Outcome	Authors/ Code	Downgrading factors for study design, risk of bias (limitations in execution) and imprecision														Upgrading factors						Overall GRADE Score	
	(Rupp et al., 2004)	*		*				*					*	*		*						3	
Lane crossing	(Sagaspe, P et al., 2008)	*	*	*		*	*	*		*	*	*	*	*								0	2.5
	(Anderson & Horne, 2013)	*						*		*		*	*								*	3	
	(Matthews et al., 2012$_{(a)}$)	*		*		*		*				*		*								0	
	(Matthews et al., 2012$_{(b)}$)	*		*		*		*	*									*				1	
	(Philip et al., 2005$_{(b)}$)	*	*	*								*		*								0	
								*		*													
	(Philip et al., 2005$_{(a)}$)	*	*	*		*		*		*	*	*		*								-1	
	(Lowden et al., 2009)	*			*	*						*				*			*			3	
	(Rupp et al., 2004)	*		*				*					*	*		*						3	
	(Filtness et al., 2012)	*											*					*	*	*		6	
	(Pizza et al., 2004)	*		*				*		*		*		*								0	

Outcome	Authors/ Code	Downgrading factors for study design, risk of bias (limitations in execution) and imprecision								Upgrading factors			Overall GRADE Score	
Mean and *SD of speed	(Pizza et al., 2004)	*		*			*	*	*		*		0	0
	(Lowden et al., 2009)	*			*	*			*			*	3	
Deviation from speed limit	(Pizza et al., 2004)	*		*			*	*	*		*		0	0.92
	(Matthews et al., 2012(a))	*		*		*	*		*		*		0	
	(Rupp et al., 2004)	*		*			*			*	*		2	
Speed variability	(Rupp et al., 2004)	*		*			*			*	*		2	1.5
	(Matthews et al., 2012(a))	*		*		*	*		*		*		0	
Speed violation	(Matthews et al., 2012(a))	*		*		*	*		*		*		0	0
Mean reaction time	(Pizza et al., 2004)	*		*			*	*	*		*		0	0.75
	(Matthews et al., 2012(a))	*		*	*	*	*		*		*		0	
	(Philip et al., 2005(b))	*	*	*		*			*		*		0	

Outcome	Authors/ Code	Downgrading factors for study design, risk of bias (limitations in execution) and imprecision										Upgrading factors				Overall GRADE Score	
							*										
	(Rupp et al., 2004)	*		*			*				*	*				2	
	(Philip et al., 2005(a))	*	*	*		*	*			*		*				0	
*SD of reaction time	(Pizza et al., 2004)	*		*			*		*	*		*				0	0
Distraction	(Anderson & Horne, 2013)	*					*			*	*				*	3	2
Steering wheel angle	(Lowden et al., 2009)	*			*	*				*			*		*	3	*NR

*SD= standard deviation, NR= Not reported

3.4.8 **Levels of the quality of the body of evidence for outcomes**

The GRADE statement classifies the quality of a body of evidence as high, medium, low, and very low quality. These levels reflect the confidence in assuming that the estimated effect is close to the true effect (Balshem et al., 2011). These levels are defined as follows:

a. High quality: high confidence that the true effect lies close to the estimated effect
b. Medium: moderate confidence the true effect lies close to the estimated effect
c. Low: limited confidence that the true effect lies close to the estimated effect
d. Very low: very little confidence that the true effect lies close to the estimated effect

The GRADE guidelines do not directly map onto the OGS for the body of evidence at the above-mentioned levels. Therefore, based on judgment, four ranges of OSG scores were assigned to each of these four quality levels. High quality evidence included all OGSs greater than or equal to 3, while scores between 2 and 3 corresponded to medium quality. Scores between 1 and 2, and scores between 0 and 1, were attributed low and very low quality body of evidence ratings, respectively. Table 3.11 represents the quality levels of the body of evidence for the outcomes.

Table 3.11 The levels of the quality of body of evidence for outcomes

Outcome measure	Quality of body of evidence			
	Very low 0<OG<1	Low 1<OG<2	Medium 2<OG<3	High 3<OG
Lateral deviation from centre of the road		*		
*SD of lateral position		*		
Lane crossing			*	
Deviation from speed limit	*			
Speed variability		*		
Mean reaction time	*			

SD = standard deviation

3.5 CONCLUSION

It is clear that there are few studies available that describe the specific effects of sleep deprivation on young driver's performance. Over the last 10 years only 10 peer-reviewed original papers on this issue have been published. It is acknowledged that there are other sleepiness-related studies within the same age group as this systematic review. Based on the inclusion criteria (Section 3.3.3) these studies were not included since the sleep loss was not the main exposure (Watling, Smith, & Horswill, 2014), the outcome measures did not include driving performance (Smith, S., Horswill, Chambers, & Wetton, $2009_{(a)}$) and participants had different age ranges (Forsman et al., 2013).

The PRISMA-based systematic search for information revealed that there are no previous reviews and particularly, no systematic reviews, available to summarise the findings of sleep loss on driving performance of young drivers.

The review of selected papers based on the GRADE guidelines revealed some important facts in the available literature as follows:

1. There is a lack of high-quality evidence provided by the available studies, with no randomized control trials (RTCs), very strong experimental designs, or large-scale studies. Most of the studies did adopt otherwise robust quasi-experimental cross-over, within-groups, or between-groups repeated measures designs.
2. There is considerable inconsistency in the available evidence due to major differences between the studies in factors such as sample sizes, the method of sleep deprivation, control for confounding factors, definition and measurement of outcomes, and the magnitudes of effects. There were also consistent flaws or omissions in the reporting of methodologies and findings.
3. Samples are often limited, with 50% of the papers including samples of fewer than 15 participants. The limited sample sizes used in these studies, and the inclusion of only male participants in 70% of studies, raise questions about the representativeness and generalisability of these findings.

4. There are differences between studies in the definition of outcomes, and some definitions were not reported. The most inconsistent definition was that for lateral position. 50% of the papers utilised this parameter, but each of them defined this parameter in a different way. This resulted in different definitions for mean lateral position, and for the standard deviation of lateral position variables. Line crossing was reported in 70% of papers, but with less inconsistency in its definition. In 40% of papers a comparable definition of crossing one of the lane markers or lines has been assumed. There were flaws in reporting the precise definitions of outcomes across studies, with 50% of studies providing poor definitions of these outcome variables.
5. Sleep deprivation paradigms also differed between the studies. In 80% of the studies, acute sleep loss was induced (but in different doses), and only 20% of papers attempted to induce a state of chronic sleep deprivation.
6. The time of day for sleep restriction in 80% of the studies was consistent (restriction occurred at the same times of circadian days), while in 20% of the studies sleep loss happened in different times of day due to the application of forced desynchrony protocols.
7. Driving conditions varied very much across the studies. 90% of studies were undertaken on a driving simulator of different types, each with various scenarios and driving tasks, while 30% of studies included on-road experiments in their protocol as well.
8. Time-of-day when driving also differed between the studies. In 50% of studies, drives were undertaken during the night time hours (Lowden et al., 2009; Matthews et al., $2012_{(a);}$ Matthews et al., $2012_{(b);}$ Rupp et al., 2004; Sagaspe, P et al., 2008).
9. The durations of drives differed, with 50% of drives between 1.5 to 2 hours, and 40% of studies with shorter durations of 10 to 30 minutes.
10. The outcomes reported in these studies were lane related variables (90% of studies), speed-related outcomes (20%), and cognitive performance outcomes (50%).
11. From lane position related outcomes, the standard deviation of lateral position was studied by 50% of papers and found to increase with sleep loss in each of these papers. The findings suggest that the standard deviation of lane position

is sensitive to time of day, prior wake period, and the day of sleep deprivation (Matthews et al., 2012$_{(a)}$). A severe or total sleep loss can increase STD of lateral position by at least 1.5 fold. It should be noted that there is limited confidence in the accuracy of these findings due to the low quality of findings. No evidence was available on the effects of chronic mild sleep loss on this outcome.

12. Findings of lane crossing were reported in 80% of the studies. These data suggest an increase of between 1.5 and 6 fold in line crossing. This effect was supported by a medium-quality body of evidence, suggesting moderate confidence in the validity of the estimated effect (and with only one measure of effect size available).
13. In 30% of reviewed papers (Matthews et al., 2012$_{(a)}$; Pizza et al., 2004; Rupp et al., 2004) after one night total sleep loss the number of speed exceedance events increased in daytime drives, however, the magnitude of speed exceedance and speed variability after partial sleep loss did not change (Rupp et al., 2004).
14. Mean reaction time (Pizza et al., 2004) and mean 10% slowest reaction time (Philip et al., 2005$_{(b)}$) both increased after acute total or chronic partial sleep loss, respectively. There is very low confidence in the findings of reaction time and their proximity to the real effect (very low quality).
15. In the reviewed papers the steering wheel variables have not been studied, but the findings of lateral position in the reviewed papers are in agreement with the findings of (Forsman et al., 2013), that standard deviation of lateral position and steering wheel are currently the most sensitive outcomes to driver's sleepiness and can result in lane crossings or hitting adjacent cars.

Based on the GRADE criteria developed in this systematic review, the two predominant groups of degrading factors for the quality of papers were the "risk of bias" and, to a much lower extent, the "imprecision" (uncertainty). From the group of risk of bias, the quality of papers suffered from flaws in measuring sleepiness and outcome measures, particularly from two sub-factors of inadequate monitoring of sleepiness while conducting the experiment and from practice effect. The small

sample size of papers was the most common degrading factor from the imprecision group. The quality of papers benefited from two upgrading factors; firstly, from "control for exposure and inclusion criteria" (mainly from strong control of sleep loss before test), and secondly from "certainty" (in particular recording the wake EEG during test and control for distraction of drivers by filming their faces).

The Overall GRADE Scores of the body of evidence for the most commonly studied variables were assigned very low-quality levels for mean reaction time and deviation from speed limit, to low-quality levels for standard deviation of lateral position, speed variability and lateral variation from centre of the road, and to medium-quality level only for lane crossing. None of the outcome measures was reported by a high-quality body of evidence.

In summary, in order to draw an explicit conclusion about the effects of sleep loss on young drivers' performance it is crucial to obtain more reliable data. This could be done by adopting common protocols and consistent metrics, ensuring adequate power in the studies, using better quality experimental designs such as RCTs for interventions, and by adopting better epidemiological methods. Additionally, the circadian and homeostatic contributors to sleepiness should be considered in developing methodologies, and certainly in understanding the variation in outcomes from published studies in which these factors vary. It is crucial to enhance the quality of studies on drivers' sleepiness by considering the GRADE criteria, as well as to report the findings based on the PRISMA statement.

Chapter 4: Review of Alerting Effects of the Light and Caffeine

This chapter provides a review of the effects of light and caffeine on driver alertness and performance. A brief overview of countermeasures for driver sleepiness is provided in Section 4.1. Section 4.2 provides a detailed review of non-visual effects of light, followed by the instantaneous alerting effects of light (Section 4.3) and the alerting effects of caffeine in Section 4.4. In Section 4.5 the alerting effects of light and caffeine are compared. Finally, a summary of the findings and their implications on this research program is provided in Section 4.6.

4.1 COUNTERMEASURES FOR SLEEPINESS

Drivers vary in their preference for using common countermeasures of sleepiness (Anund et al., $2008_{(a)}$) such as opening the window, stopping and taking a walk, listening to the radio or a passenger, napping and taking caffeine (Maycock, 1996). The three first strategies are regarded as ineffective (Heatherley, 2011; Horne, J.A & Reyner, 1996; Reyner, L. & Horne, 1998). Napping, while potentially effective, may cause "sleep inertia" upon awakening, observed as difficulty in arousing and "thick headedness" (Horne, J.A & Reyner, 1996, 2001; Phipps-Nelson, Redman, Schlangen, & Rajaratnam, 2009; Reyner, L. & Horne, 1998). Caffeine is regarded as a more feasible intervention (Dunwiddie & Masino, 2001; Fredholm, Bättig, Holmén, Nehlig, & Zvartau, 1999; Horne, J.A & Reyner, 1996; Mets et al., 2012; Reyner, L. & Horne, 1997; Reyner, L. & Horne, 2000). Recently, some researchers have examined the effects of night or daytime exposure to light on driving tasks as a potential countermeasure for driver sleepiness (Phipps-Nelson, Redman, Dijk, & Rajaratnam, 2003). The effects of light and caffeine as two more effective countermeasures for driver sleepiness are explained in detailed as follows:

4.2 NON-VISUAL EFFECTS OF LIGHT

Light has been found to elicit direct and indirect neurobiological effects beyond vision. Light has some indirect long-term (phase shifting) effects on human circadian rhythms and hence, some human psycho physiological functions regulated by circadian rhythms such as sleep-wake cycle, core body temperature, melatonin secretion, alertness and performance (Figueiro, M.G et al., 2007a; Stephenson et al., 2012). The mechanisms of human circadian sleep/wake and alertness were described in Chapter 2. Apart from these long term effects, light also directly elicits some instantaneous changes in physiological arousal and performance (Smolders et al., 2012; Stephenson et al., 2012; Thessing et al., 1994). Phase-shifting effects and immediate effects of light on alertness and performance are explained here.

4.2.1 **Circadian phase-shifting effects of light**

Light exerts indirect physiological effects on the circadian rhythm via temporal phase shifting of the circadian clock (An, Huang, Shimomura, & Katsuura, 2009; Figueiro, M.G et al., 2007a; Lockley et al., 2006; Revell et al., 2006; Rüger et al., 2006; Stephenson et al., 2012; Thessing et al., 1994). Body temperature and melatonin levels are common markers of circadian rhythm. The endogenous rhythm of body temperature represents the circadian component of sleepiness, with maximum sleepiness occurring 1-2 h after the minimum of body temperature (Leproult, Van Reeth, Byrne, Sturis, & Van Cauter, 1997). The phase-shifting effect of light can only be detected in the longer term (i.e. in the next circadian cycle) (Vandewalle et al., 2009).

Light is capable of resetting the phase of the circadian pacemaker and synchronising the intrinsic period of the human circadian pacemaker to a 24 h day (Klerman, Dijk, Kronauer, & Czeisler, 1996). Depending upon the precise time of exposure to light, circadian phase of melatonin production or minimum core body temperature will be altered. Light exposure before minimum core body temperature induces phase delays (e.g. minimum CBT occurs at a later times) and after minimum CBT causes phase advances in the pacemaker (e.g. minimum CBT occurs at an earlier time) (Appleman et al., 2013; Cajochen, Christian, Brunner, Kräuchi, Graw, & Wirz-Justice, 2000; Figueiro, M.G et al., 2007a; Klerman et al., 1996; Münch et al., 2012). In type 1

(weak phase shift) PRCs, light exposure at the time of minimum CBT, even in consecutive days, does not change circadian phase, but attenuates amplitude of the circadian pacemaker (Klerman et al., 1996; Postolache & Oren, 2005). However, the type 0 PRCs (strong phase shift) may be established by consecutive light exposure, with the first exposure suppressing the amplitude and making the circadian rhythm more sensitive to the second exposure (Postolache & Oren, 2005). In type 0 PRC, phase shifts as large as 12 hours have been reported when light is centred at the time of minimum temperature (Czeisler et al., 1989; Postolache & Oren, 2005).

The phase shifting capability of light has been utilised to shift the circadian phase of shift workers to help them cope with work hours. The phase delaying effects of a single-beam bright light are dependent on the duration of exposure. For instance, a 4-h night time exposure to bright light at more than 9000 lux was able to reduce objective sleepiness (Multiple Sleep Latency Test) and performance (Simulated Assembly Line Task) for a considerable time, even during subsequent nights, while a 2-hour exposure to the same amount of light does not produce the same effects (Thessing et al., 1994). Therefore, in simulated night-work studies some researchers have confirmed that precise timing of bright light/dark, and/or combination of bright light during night shifts and the scheduled daytime sleep/dark could result in approximately 7 h phase delays in circadian rhythms of shift workers (Horowitz et al., 2001; Smith, M. R. et al., $2009_{(a)}$). Some even incorporate days off in light dark schedule (Smith, M. R. et al., 2008). There are however, some practical issues regarding application of these schedules in real life, in that most permanent night-shift workers (e.g. commercial drivers) are not interested in changing their normal day-oriented circadian rhythm to a night-oriented rhythm, particularly on days off due to their social and family lives (Figueiro, M.G et al., 2007a; Smith, M. R. et al., 2008). Additionally, long time control of strict light/dark and sleep schedules is not plausible (Figueiro, M.G et al., 2007a). As a result, consideration of the acute direct alerting effects of light appear more reasonable (Figueiro, M.G et al., 2007a; Lowden, Åkerstedt, & Wibom, 2004).

4.3 INSTANTANEOUS ALERTING EFFECTS OF LIGHT

Apart from light phase shifting properties, exposure to bright light has a direct alerting effect in humans (Phipps-Nelson et al., 2003).

Figure 4.1 shows brain areas involved in the alerting effects of light. A network of areas around the pulvinars (red) mediates the effects of light on alertness and cognition. Light can affect brain function and cognition by activating alertness-related pathways in sub cortical structures (e.g. hypothalamus, brainstem, pulvinars). Light rapidly affects the hypothalamus (blue) and pulvinars (green) and after the first little seconds the brainstem (yellow) starts to respond to light. The hypothalamus, amygdala, and the temporal cortex are mood-related pathways in limbic areas and are responsible for emotional changes from exposure to light. The cortical areas involved in the ongoing cognitive process then respond to the light and subsequently affect performance.

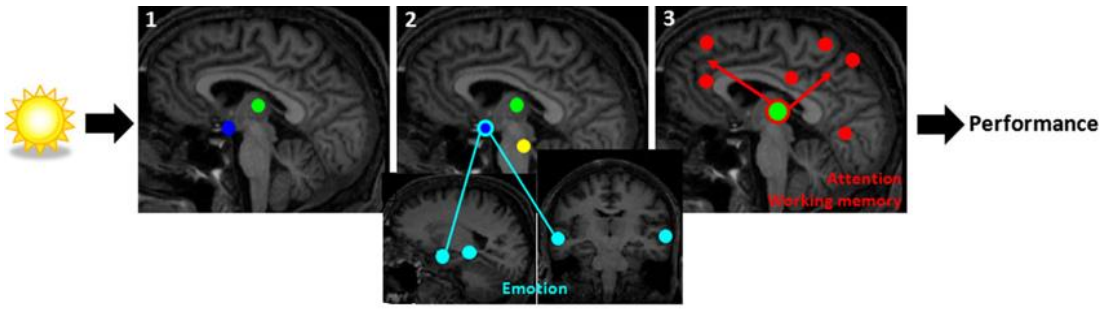

Figure 4.1. Different brain areas instantaneously responding to light (adopted from Vandewalle et al., 2009).

Regardless of the time of day, the magnitude of alerting effects of bright light depends on dose (illuminance levels), wavelength , duration of lighting, level of prior exposure to light (Chang, Scheer, Czeisler, & Aeschbach, 2013), and endocrine and electrophysiological variations of alertness (Leger, Philip, Jarriault, Metlaine, & Choudat, 2009). Higher intensities, longer durations, and shorter wavelengths (blue) of light have more alerting effects (Chellappa et al., 2011; Smolders et al., 2012; Vandewalle et al., 2009).

In humans, intrinsically photosensitive retinal ganglion cells (ipRGCs) are responsible for the nonvisual alerting effects of light. The ipRGCs have peak sensitivity to 480 nm light (perceived as blue light, see Figure 4.2). This wavelength is shorter than peak sensitivity of most other photoreceptors in the retina, with the rods (R), S cones, M cones, and L cones having their peak sensitivities at ~500 nm, ~420 nm, ~530 nm and ~560 nm, respectively (Hatori & Panda, 2010). Other wavelengths can also drive ipRGCs, just at higher intensities as indicated by the distribution of their spectral response curve (Zele et al., 2011).

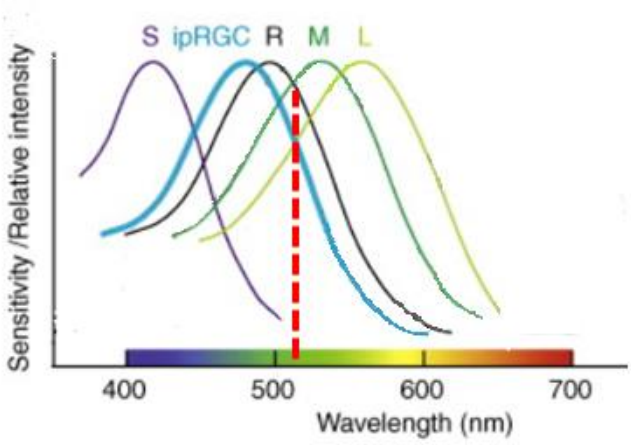

Figure 4.2. Spectral sensitivity of rod, cones (S, M & L) and ipRGCs; dashed line indicates 520 nm light provided by the RE-Timer devices (modified version adopted from Hatori & Panda, 2010).

Analysis of lighting conditions adopted in both night time and daytime studies suggests that blue light has been used mostly in the frequency range of 450-470 nm, in low levels from 1 to 40 lux, whereas white light (broad spectrum) has been used in high levels (up to 10000 lux). Red light has been mostly adopted in the frequency range of 630-640 nm, with approximately the same level as blue light (1- 40 lux).

Light experiments vary in light intensities, duration of exposure, wavelength, timing of administration and target study group. In line with the research questions of this study and the associated hypotheses, the alerting effects of light in relation to objective, subjective, cognitive performance and driving performance outcomes of sleepiness are described below

4.3.1 **Alerting effects of the light on objective sleepiness outcome measures**

Effects of the light on EEG-related outcome measures

Evidence shows that objective outcomes of sleepiness such as EEG and ECG related outcomes are sensitive to light. Alerting effects of light on different human sleepiness indicators have been mostly examined during the night to provide the greatest declines in alertness in both the circadian and homeostatic drives. Very few of these studies have examined the alerting effects of light in the driving context.

Figueiro et al. (2009) reported that a 45-minute nocturnal exposure to diffused blue light (470 nm) at two irradiances of 40 μw/cm^2 (40 lux) and 10 μw/ cm^2 (at 10 lux) could significantly decrease the EEG relative alpha power and increase relative beta power when compared with dim red light (< 1 lux), with a larger effect of 40 lux blue light. Decreases in the EEG alpha power and increase in beta power suggest an alerting effect of blue light. Figueiro et al. (2009) also reported that low levels of blue light (40 lux) could increase heart rate variability.

Cajochen (2000), reported that in the last 90 min of 6.5-h night time exposure to light, EEG alpha-theta frequencies (5-9 Hz) showed greater decreases under 106 lux and 9100 lux than under 3-lux light ($P < 0.002$). They concluded a steep dose-response relationship between light level and EEG alpha-theta power density.

Phipps-Nelson (2009) in a simulated night-time driving experiment compared the effects of 5 h (from 23:55 to 05:30) exposure to three counterbalanced lighting conditions with 2 h ambient light conditions from 20:40 to 23:30. Lighting conditions included blue light (460 nm, 2 m W/cm^2, with 1.12 to 1.15 lux in the horizontal angle of gaze in the driving cabin), red light (620 nm, 1.13 to 1.18 lux) and ambient light (430 nm and 620 nm, 0.5 m W/cm^2, 0.02 to 0.20 lux). Light condition had a significant effect on theta activity ($F_{2,12} = 9.76$, $p = 0.003$), but not on alpha activity. Blue light reduced theta activity both during ($p = 0.031$) and after light exposure ($p = 0.030$) when compared to ambient light.

Some studies have reported the dependence of alerting effects of light on time of day after comparing night time exposure to light with daytime exposure.

In a constant routine study, Badia, et al. (1991) examined the effects of both night time and daytime exposure to bright white light (ranging from 5000 to 10,000 lux at the cornea) on EEG activity in alpha, beta and theta frequencies. The study involved four experiments with different groups of participants: 1) night time alternating bright light-dim light conditions in which participants were exposed to 90-min blocks of alternate bright light (5000 lux to 10,000 lux) or dim light (50 lux), 2) daytime alternating bright light-dim light condition as the control condition in which participants received two 90-min blocks of alternating bright light and dim light, 3) night time continuous bright light conditions in which participants were randomly exposed to only one bright light condition - either continuous night time bright light (5000 to 10,000 lux) or continuous night time dim light (50 lux) condition, and 4) night time continuous dim light condition. Comparison of the effects of night time bright light and dim light in participants exposed to alternating bright light (5000 lux to 10,000 lux white light) and dim light (50 lux) conditions revealed that bright light increased the log power density of EEG beta, but not power of alpha and theta bands, indicating alerting effect of bright light. A similar pattern in EEG differences was observed among the daytime alternate condition (control) group; however, the differences were not significant. This study implies that night time alternating bright light-dim light conditions exert more alerting effects in terms of EEG frequencies than daytime alternate bright light-dim light or daytime continuous bright light conditions.

Rüger, et al. (2006), examined the effects of daytime and night time bright light exposure on heart rate using the results of three experiments involving a 4 h exposure to different light intensities (<10, 100 and 5000 lux), at various times (midnight till 4:00 a.m. versus noon till 4:00 p.m.), and at different retinal areas exposed to the light (whole retinal versus partial retinal exposure). Participants were classified into two groups based on time of exposure (daytime experiment or night time experiment). During the daytime experiment participants were exposed to bright light (5000 lux) or dim light (10 lux) from noon until 4:00 pm. During the night time experiment participants were exposed to either bright light (5000 lux) or dim light (10 lux) from midnight until 4:00 a.m. They found that regardless of whole or partial retinal exposure to bright light, heart rate increased under night time bright light $F_{1,11}$

= 22.9, p = 0.001, compared to daytime exposure with no such an effect $F_{1,11} = 0.2$, p = 0.604. The increase in heart rate is associated with increased alertness levels.

An, et al. (2009) compared the time-of-day (daytime or night time) dependent effects of two monochromatic lights (with different wavelengths at 458 nm or 550 nm), but the same irradiance density (9.8 m W/cm^2 at eye level) on human EEG activity and visual PPVT reaction time (RT). Monochromatic lights were delivered at two times (daytime and night time), 12 h out of phase with each other with day time exposure 9 h after awakening. Findings of this study showed that the Alpha Attenuation Coefficient (AAC) at night was higher than in the daytime ($F_{1,11} = 10.89$, $p < 0.01$), suggesting that the participant levels of arousal at night time were higher than in the daytime.

Few studies have been conducted in the daytime. Recently Okamoto et al. (2014) in a daytime study investigated the alerting effects of 48 min exposure to either blue light or red light or darkness on nine individuals after one-night sleep loss for 1.5 h in the early morning. They did not find any significant effects of light condition on EEG alpha and theta power densities. However, the EEG alpha power was lower under both blue and red lights when compared to the placebo (darkness) conditions 30, 40 and 50 min after starting the experiment. In contrast, a main effect of time interval was found for theta with the EEG theta power being larger at 30, 50 and 60 min after starting the experiment. These findings show that both blue and red light could improve alertness by reduction of alpha activity after 30 min. The increase in theta activity shows increased sleepiness and the ineffectiveness of these two lights on this indicator of sleepiness.

Overall, the alerting effect of light on objective sleepiness outcome measures have been shown by decreased alpha and theta activities, increased beta activity and heart rates. The findings also imply that the alerting effects of light exposure on human objective sleepiness depend on the wavelength and level of light, in that shorter wavelengths of light elicit more stimulating effects and need lower intensities to exert their alerting effects. Finally, the alerting effect of light depends on time of day with night time bright light producing more alertness than daytime exposure.

Alerting effects of light on PPVT outcome measures of sleepiness

Many studies have reported the sensitivity of the psychomotor vigilance task (PPVT) to the alerting effects of light.

In a between-participant experiment, Lafrance et al. (1998) examined the stimulating effects of daytime exposure to white bright light on daytime vigilance (during and after exposure to light) among 14 participants (10 women, 4 men; 19–24 years old). Participants were involved in the experiment for four days at home and 4 days/6 nights in the laboratory. Participants were given two nights of 4 h sleep restriction before being exposed to a 4.5 h bright light (a white light of about 10,000 lux at eye level) or red dim light (a red light of about 100 lux) during the late morning on two consecutive days. Findings of this study showed that two nights of sleep restriction did not affect their performance due to a high practice effect. A significant day effect on mean reaction time was observed only in the bright light group ($p < 0.0001$). There was a significant decrease of RTs from the pre-light day to day 1 and day 2 of light exposure ($p < 0.05$). There was also a significant day effect on percentage of errors in the bright light group ($p = 0.01$) but in a different direction. There was a significant increase in percentage of errors from the pre-light day to day 1 and day 2 of light exposure ($p < 0.05$). The authors concluded that daytime bright light and red dim light could improve global performance, but changed the method of performing PPVT (seen as faster reaction times and increased percentage of errors in bright light).

Phipps-Nelson (2003) found a significant main effect of 5 h daytime exposure to bright light (1000 lux) on PPVT mean reaction times after two nights of 3 h sleep loss ($F_{1,13} = 5.014$, $p < 0.05$). Bright light reduced the mean reaction times, but dim light (< 5 lux) increased mean RTs. They also confirmed that PPVT reaction time improved immediately after exposure to light. A later study by Phipps-Nelson (2009) reported a significant effect of light conditions on PPVT reaction times ($F_{2,14} = 4.42$, $p = 0.032$), and PPVT lapses ($F_{2,14} = 3.89$, $p = 0.048$). They reported that mean reaction time was faster under 5 h exposure to blue light (2 mW/cm^2, from 1.12 to 1.15 lux) than ambient light (0.5 mW/cm^2 from 0.02 to 0.20 lux) both during ($p = 0.038$) and after light exposure ($p = 0.048$). In contrast, they reported an increase in PPVT lapses under all light conditions ($F_{3,21} = 3.89$, $p = 0.048$).

Smolders et al. (2012) examined the alerting and vitalizing effect of daytime exposure to bright light under natural conditions (no sleep loss or pre-experiment dim light). Participants had a short (> 30 min) exposure to less than 1000 lux white light with colour temperature of 4000 k during two experimental sessions (morning and afternoon sessions, each session lasting for 90 min). During a 30 min baseline phase, when participants were exposed to 200 lux (4000 k) at work level, two cognitive performance tests were measured including a 5 min auditory PPVT (mean reaction time, 10% slowest responses and 10% fastest responses), and a Necker cube pattern control task (number of errors and percentage correct). During a 1 h experimental phase (four 15 min blocks of counterbalanced light exposure to either 200 lux or 1000 lux at eye level) all measurements of the baseline phase were repeated (except the second performance test). During blocks 1, 2, and 3, letter digit substitution tests (LDST, the number of correctly substituted digits) were undertaken followed by an auditory PPVT. Exposure to 1000 lux bright light shortened reaction times (PPVT) when compared with light of 200 lux. The effects of light on PPVT were modulated by time of day and duration of the experiment. The most pronounced effect of illuminance on PPVT was observed in the morning and/or towards the end of the experiment. In this study, light exerted alerting effects even during the daytime. Therefore, the authors hypothesised that in addition to the circadian system, alerting and vitalizing effects of light might be elicited by other mechanisms through the activation and modulation of alertness-related (e.g. brainstem, thalamus) and mood-related pathways (e.g. amygdale, hippocampus).

These findings suggest that all outcomes of cognitive performance do not consistently respond to light. The effects of light on performance depend on the type of test with some performance tests, such as PPVT, being more sensitive to bright light.

4.3.2 **Alerting effects of the light on subjective sleepiness outcome measures**

Subjective sleepiness normally shows sensitivity to the alerting effects of light. Cajochen, et al. (2000) found an immediate improvement in subjective sleepiness in 9100 lux compared to 106-lux and 3-lux lights. They suggested a dose-response relationship between levels of light and subjective sleepiness. They found that KSS

was less deteriorated during 6.5 h night time exposure to 9100 lux and 106 lux than dim light (3 lux). They also reported that subjective sleepiness in the high (9100 lux) and mid-light-level (106-lux) groups deteriorated during the 2 h after exposure to light and reached the sleepiness level of the low-light-level group.

Lockley et al. (2006) in a between-groups study, randomly assigned participants to a 6.5 h 460 nm (n = 8) or 555 nm (n = 7) monochromatic light starting 9.25 hours before their respective wake time. They found no significant difference in KSS scores between the two groups (460 nm, n = 8; 555 nm, n = 7) at the onset and during light exposures and for up to 1 h after exposure ended. However, sleepiness increased in both groups after that time coinciding with the circadian nadir in alertness.

Phipps-Nelson (2003) compared the alerting effects of 5 h daytime (from noon to 5 p.m.) exposure to 1000 lux bright light with dim light on two groups of participants after two nights of 5 h sleep (delayed bed times). They found a significant main effect of light group on subjective sleepiness (KSS) ($F_{1,13} = 6.258$, $p < 0.05$), with subjective sleepiness decreasing under bright light and increasing under dim light. Interestingly, they did not observe the improvement of KSS immediately after exposure to light, but one hour after receiving bright light.

Findings of the study by Rüger et al. (2006) showed improving effects of bright light (5000 lux at the whole retina) on subjective sleepiness (KSS), both in the daytime and at night. This study found an interaction effect between light condition and retinal exposure ($F_{1,22} = 16.8$, $p < 0.001$). They suggested that regardless of time of exposure (night time vs. daytime), whole retina exposure to bright light (5000 lux) can decrease subjective sleepiness (KSS).

A study conducted by Figueiro et al. (2009) found that light could not improve subjective sleepiness. The researchers reported that in their study involving a 45 min counterbalanced night time exposure to one of four lighting conditions of blue or red light at two levels (40 lux, 10 lux), subjective sleepiness (KSS) was not significantly changed when 30 min measured after exposure to these light conditions. In the study of Phipps-Nelson (2009)a significant increase in subjective sleepiness was observed during 6 h night time exposure to blue light (460 nm, 2 mW/cm^2, from 1.12 to 1.15

lux) when compared to ambient light (430 nm and 620 nm, 0.5 mW/cm^2 from 0.02 to 0.20 lux) ($F_{2,14} = 20.13$, $p < 0.001$).

These findings suggest that bright light generally decreases subjective sleepiness during both night and daytimes.

4.3.3 **Alerting effects of light on driving performance outcome measures**

There is little evidence available regarding the alerting effects of light on driving performance of sleep-deprived drivers. One of the available study is the simulated driving study of Phipps-Nelson (2009) examining the alerting effects of 6 h night time exposure to counterbalanced blue light (460 nm, 2 mW/cm^2, 1.12- 1.15 lux), red light (620 nm, 1.13-1.18 lux) and ambient light (430 nm and 620 nm, 0.5 mW/cm^2, 0.02 to 0.20 lux) on driving performance outcomes. They found that unlike the alerting effects of light on objective measures (theta activity) and mean reaction times, there was no main effect of light conditions on driving simulator performance (lateral lane deviations) ($F_{2,14} = 17.10$, $p < 0.001$). Instead, lateral lane deviations became progressively worse across the night under all light conditions.

Two studies have compared the alerting effects of light and caffeine on different outcomes including driving performance outcomes. In one of these studies, night time administration of the combination of bright light (10000 lux) and 200 mg of caffeine decreased lane drifting by sleep-deprived participants during simulated night time driving (Hartley et al., 2013). In the other study, the effect of the administration of light on driver performance was compared to the effect of caffeine. Continuous nocturnal blue light (468 nm) improved on-road driving performance more than 200 mg of caffeine or the caffeine placebo (Taillard et al., 2012). These two studies are explained in more detail in Section 4.5.

4.4 CAFFEINE

Caffeine (1, 3, 7-trimethylxanthine), reaches its maximum plasma concentration within 15 to 120 min (Arnaud, 1987), or an average of 30 minutes after consumption (Blanchard & Sawers, 1983; O'connell & Zurzola, 1984), and can be absorbed

completely by the body after around 45 min (Blanchard & Sawers, 1983). Studies have revealed complex alerting and stimulating effects for caffeine depending on dosages, participants and experimental conditions (Lorist & Tops, 2003). Generally, caffeine has been shown to restore performance to initial levels during circadian dips in alertness or after sleep loss (Nehlig, 2010; Smith, A., 2002). The stimulating action mechanism of caffeine is generally regarded as an antagonism of a mediator of sleep, adenosine, particularly by blocking adenosine A1 and A2A (Fredholm et al., 1999).

According to Denaro (1990), 4 mg/kg/day (e.g. 240 mg/day for a 60 kg individual) and 12 mg/kg/day are regarded as low-dose and high-dose caffeine levels, respectively. Several driving experiments have demonstrated that taking 100–300 mg, found in 1-3 average cups of coffee or two cans of "energy" drinks such as "Red Bull", can enhance performance and reduce subjective sleepiness in both driving simulators (De Valck & Cluydts, 2001; Horne, J.A & Reyner, 1996; Reyner, L. & Horne, 1997; Reyner, L. & Horne, 2000), and on-road studies (Philip et al., 2006; Sagaspe, Patricia et al., 2007) among sleep deprived participants. Similarly, lower doses of caffeine (one cup containing 80 mg caffeine), as predominantly consumed in real life, appear to (1) enhance driving performance as measured by the standard deviation of lateral position (SDLP) and the standard deviation of speed, and (2) reduce mental effort and subjective sleepiness in a prolonged simulated highway driving among non-sleep deprived individuals (Mets et al., 2012). A recent case-control study among long-distance commercial drivers also revealed that drivers who had consumed caffeinated beverages such as tea, coffee, and energy drinks were about 63% less likely to have a crash compared with non-consumers of caffeine (Sharwood et al., 2013). These alerting effects of caffeine mostly appear 30 min after consumption and last for an hour or so depending on the level of sleepiness (Blanchard & Sawers, 1983; Horne, J.A & Reyner, 2001; O'connell & Zurzola, 1984). Some other forms of caffeine, such as caffeinated gum, have been used by Snel & Lorist (2011). These authors found that after oral ingestion of caffeine, 99% of it was absorbed from the gastrointestinal tract into the bloodstream with maximum levels reached between 45 and 80 min post-administration. There is discrepancy about the washout period of caffeine. Some researchers considered a period of 12 h (Brunyé, Mahoney, Lieberman, Giles, & Taylor, 2010). Others have considered a 3

day washout for caffeine (Giles et al., 2012). Caffeine plasma half-lives also found to vary from 2.7 to 9.9 h due to substantial inter-individual differences in its elimination (Blanchard & Sawers, 1983).

In most studies participants were under acute caffeine withdrawal before starting the experiment. Hence, some researchers attribute the alerting effects of caffeine to withdrawal reversal rather than a net beneficial effect of caffeine (Heatherley, 2011; Rogers, P.J et al., $2005_{(b)}$). In one study researchers included a one-week washout period to eliminate any effects of caffeine withdrawal. They found that even individuals who were withdrawn for a week showed alerting effects of caffeine (Smith, A., Sutherland, & Christopher, 2005).

Overall, the literature supports the alerting effects of caffeine. Nevertheless, it is not a reliable countermeasure since it has a temporary effect and its consumption depends on personal preferences. Additionally, caffeine has some side effects on the upcoming recovery sleep after sleep loss such as increased sleep onset latency (Carrier et al., 2007), decreased sleep efficiency, decreased sleep duration and REM sleep (Carrier et al., 2007). Table 4.1 shows the characteristics of light/caffeine interventions in some related studies. Table 4.2 represents a summary of the reviewed studies on the effects of light.

Table 4.1 Characteristics of light/caffeine interventions in some related studies

Authors	Light colour / wavelength Caffeine dose	Timing and duration of exposure/caffeine consumption	Light irradiance/illuminance	Placebo condition	Distance from the eye
Taillard et al. (2012), Night time drive	blue light at 468 nm ± 8 nm, Caffeine 200 mg,	Caffeine or placebo of caffeine intake, 2 h driving under blue light, caffeine or caffeine placebo intake during 15 min break, 2 h driving under blue light,	7.4 mw/cm^2 (in order of 20 lux) at eye level,	Placebo caffeine 15 mg,	75 cm from participant's eye,
Hartley et al. (2013), Night time simulated drive	polychromatic white bright light, One dose of caffeine (200 mg),	30 min counterbalanced exposure to caffeine plus bright light, caffeine plus bright light placebo, caffeine placebo plus bright light, and caffeine placebo plus bright light placebo,	Bright light 10,000 lux at eye level,	placebo white light, 50 lux at eye level, Placebo caffeine,	30 cm from participant's eye,
Figueiro et al. (2009), Night time retinal light	Diffused blue light, 470 nm Diffused red light, 630 nm,	45 min in dim red light (darkness) before a 45 min counterbalanced exposure to one of 4 lighting conditions - blue or red light at 40 lux and 10 lux. Exposure to both levels of the same spectrum in each session,	Two light boxes (0.6 x 0.6 x 0.6 m) with light-emitting diodes (LEDs) distributing blue light peaked at 470 nm (40 μw/cm^2 at 40 lux, 10 μw/ cm^2 at 10 lux), Two boxes emitted red light peaked at 630 nm (19 μw/cm^2 at 40 lux and 4.7 μw/cm^2 at 10 lux), Light illuminances and irradiances	Dim red light (< 1 lux),	Very close to light box, ensuring exposure to retinal intensity,

Authors	Light colour / wavelength Caffeine dose	Timing and duration of exposure/caffeine consumption	Light irradiance/illuminance	Placebo condition	Distance from the eye
			were at corneal levels,		
Lockley et al. (2006), Night time	Blue light, 460 nm, Yellow light, 555 nm,	A fixed gaze for 90 min in the light before a free gaze for 10 min 6.5 h,	Blue light 12.1 µW/cm^2 photon densities (2.8 x 10^{13}photons cm-^{2} s^{-1}), Yellow light at 10.0 µW/cm^2 and equal photon density to blue light		
Phipps-Nelson et al. (2009), Night time light	Dim, narrowband blue light, 460 nm, Red light, 640 nm Dim (white) light, broad spectrum,	6 h night time exposure to counterbalanced blue, white or red light included in the 9 h test session at night time,	Blue light with spectral peak of 460 nm, 2 mW/cm^2, from 1.12 to 1.15 lux in the horizontal angle of gaze in the driving cabin, Red light with spectral peak of 620 nm ranged from 1.13 to 1.18 lux in the driving cabin, Ambient light with spectral peaks at 430 nm and 620 nm, 0.5 mW/cm^2 from 0.02 to 0.20 lux,	Red light (placebo), 640 nm,	The ambient light in the driving cabin produced by projector, blue and red lights delivered by light-emitting diode (LED) located across the simulator dashboard display,
An et al. (2009), Daytime and night time	Blue light, 458 nm	Counterbalanced monochromatic light exposure either at blue or yellow light for daytime and night-time, with 12 h out of phase with each other,	Blue light at 9.8 m w/cm^2 (at eye level),		30 cm distance from eye,

Authors	Light colour / wavelength Caffeine dose	Timing and duration of exposure/caffeine consumption	Light irradiance/illuminance	Placebo condition	Distance from the eye
Cajochen et al. (2000), constant routine, Night time light exposure	Single illuminance	The timing of light exposure was determined by an on-line core temperature assessment, participants were randomly exposed to a 6.5 h single illuminance, ranging from 3 to 9100 lux, being cantered 3.5 h before their expected CBT minimum (23:00-5:30) and ending 0.25 h before their expected CBT minimum,	Single illuminance ranging from 3 to 9100 lux,	*NA	Not reported,
Okamoto et al. (2014), within-subject repeated measures design day time study	Blue light, 470 nm, Red light, 630 nm	Three test sessions at one week intervals, In each session first darkness for 12 min, exposure to one of 3 counterbalanced light conditions (blue, red or no light) for 48 min (from 7 to 8 a.m.),	Two light boxes (0.6 x 0.6 x 0.6 m) with light-emitting diodes (LEDs) distributing blue light peaked at 470 nm (40 $\mu w/cm^2$ at 40 lux) and red light peaked at 630 nm (19 $\mu w/cm^2$ at 40 lux)	Darkness <0.01 lux,	Very close to light box, ensuring exposure to retinal intensity,
Phipps – Nelson et al. (2003)	Bright light, 1000 lux	8 participants were exposed to dim light from 9 a.m. to noon, bright light from noon till 5 p.m., dim light from 5 to 9 p.m.	The bright light (mean = 1,056 lux, range = 1,000, lux - 1,100 lux) presented by 6 fluorescent tubes,	Dim light <5 lux,	Dim light (lamps behind the participant).

Authors	Light colour / wavelength Caffeine dose	Timing and duration of exposure/caffeine consumption	Light irradiance/illuminance	Placebo condition	Distance from the eye
The mixed factorial design		8 participants were only exposed to dim light for the entire day,	Dim light, provided by standard lamps with 40-watt incandescent,		Bright light (1.5 m in front of participant at eye),
Badia et al. (1991), Constant routine, within participants	Bright light, Dim light,	4 groups with 4 lighting conditions: 3 groups at night under 9 h constant routine and one group in day as control group: Night time counterbalanced alternating BL-DL condition: six 90 min blocks of alternating bright light (5K lux to 10K lux) and dim light (50 lux), Night time continuous bright light: six 90 min blocks of bright light Night time continuous dim light: six 90 min blocks of dim light Daytime alternating BL-DL condition, starting at 1 p.m.: two 90 min blocks of alternating bright light and dim light,	Fluorescent 40 W cool white lamps to produce bright light 5000-10000 lux, and dim light 50 lux,	Daytime alternating BL-DL condition,	Lights were placed in front of the participant 46 cm from the face,
Rüger et al. (2006), Between groups	Bright light,	Randomized assignment of participants in two groups for two times of exposure to 4 h of bright light: one group between noon and 4:00 p.m. (daytime experiment) and another	Bright light boxes delivering 5,000 lux in the direction of gaze at eye level, Dim light emitted from the personal	Dim light (<10 lux),	Not reported,

Authors	Light colour / wavelength Caffeine dose	Timing and duration of exposure/caffeine consumption	Light irradiance/illuminance	Placebo condition	Distance from the eye
design, Night and day		group between night and 4:00 a.m. (night time experiment), with 1-3 washouts between two sessions,	computer without the lamps being turned on (<10 lux),		
An, et al (2009), Repeated measures within participant design	Monochromatic light 480 nm, Monochromatic light 550 nm,	Monochromatic light exposure for two times (daytime and night time), 12 h out of phase with each other with day time exposure 9 h after awakening, Each test session: 5 min exposure to standard light (19 lux on vertical surface and 96 lux on horizontal surface at eye level), dark adaptation (<1 lux) for 5 min followed by counterbalanced light exposure either at 458 nm or 550 nm,	Monochromatic light generated by a variable voltage (0–100) halogen lamp 30 cm away from the eye, and filtered by interference filters in to 458 nm or 550 nm with irradiance of 9.8 m w/cm^2 at eye level,	NA	Monochromatic light 30 cm away from the eye
Lockley et al. (2006), Constant routine	Monochromatic light 460 nm, Monochromatic light 555 nm,	During three baseline days ambient light was 190 lux, From midday of the third day of baseline period ambient light < 2 lux till the end of study, randomly assignment of participants to 6.5 h either 460 nm (n = 8) or 555 nm (n = 8) monochromatic light (±10 nm half-peak	Three 4100K fluorescent lamps distributed irradiance 10.0µW/cm^2 and 12.1 µW/cm^2 for 555 nm and 460 nm, respectively, generating an equal photon density of 2.8 x 1013 photons· cm-2· s-1 for both lights at eye level,	NA	Ceiling-mounted fluorescent lamps

Authors	Light colour / wavelength Caffeine dose	Timing and duration of exposure/caffeine consumption	Light irradiance/illuminance	Placebo condition	Distance from the eye
		bandwidth), starting 9.25 hours before their respective wake time (approximately 6.75 h before minimum core body temperature) on day 6,			
Lafrance et al. (1998), Repeated measures, between-groups	bright light, dim red light,	Expose the participants to a 4.5 h either bright light (10,000 lux at eye level) or dim red light (100 lux) on 2 consecutive days (in the late morning with no effects on melatonin secretion or on the circadian phase) after 2 nights of sleep restriction,	Bright white light (mean 12000 lux), Dim red light (mean 100 lx), The room light intensity below 50 lux at all other times,	NA	Three panels 62 x 61 cm delivered bright white light over the entire visual field at participant eye level, Dim red light was distributed by red filters,

*NA= Not applicable

Table 4.2 Summary studies of alerting effects of light

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
Figueiro et al. (2009), repeated measure cross-over (within participant) study	Comparison of effect of night time exposure to both blue and red light on human subjective and objective measures of alertness, on performance and on melatonin levels	16 participants (21 to 46 years of age)	No prior sleep loss, extended wake at night time	The EEG relative alpha power, relative beta power, ECG, Saliva melatonin, Subjective sleepiness (KSS), A battery of three psychomotor vigilance tests: a simple reaction times (RT) test, a two-choice reaction time (TCRT)	from 23:00 **Two times:** first 45 min inactivity in darkness, In the last 15 min of data collection (EEG, Performance and saliva melatonin, 45 min either 40 lux or 10 lux of either blue or red light, **One time:** 45 min inactivity in darkness (dim red light), The last 15 minutes of darkness data collection (EEG, Performance and saliva melatonin),	Effect of blue and lights on relative the EEG the EEG alpha power $F_{7,91}= 2.15$, $p = 0.046$ and on beta power $F_{7,91}=3.91$, $p < 0.0009$ as opposed to dim light, A significant decreasing impact of both 10 lux and 40 lux blue light and only 10 lux red light on relative the EEG the EEG alpha power, A significant increasing impact of both 10 lux and 40 lux blue light and only 10 lux red light on relative beta power, A dose-response relationship between blue light illuminance and changes in relative alpha and beta powers, A significant increase in heart rate by higher level (40 lux) of both blue and red light compared to ineffective lower level (10 lux) of the two spectra, No significant effect of all spectra and intensities of light conditions on performance measures (PPVT) and KSS,

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
				test, a matching-to-sample (MTS) test,		
Phipps-Nelson et al. (2009), within-subjects design, Simulated night time driving	Comparison of effects of night-time exposure to low-intensity blue light with red light and dim broad spectrum low intensity ambient white light on human sleepiness and	8 participants (5 males/3 females) aged between 23 and 43years	After two weeks normal sleep, one-night total sleep loss	EEG (delta, theta, and alpha activity), EOG (Slow Eye Movements); recorded by 4-min Karolinska Drowsiness Test (KDT, eyes open), Salivary melatonin, KSS (pre- and post-drive), Auditory	Each test session lasted for 9 h during night, From 20:40 to 23:30 pre-light test battery under ambient white light condition including Saliva, PPVT, KDT, KSS, 2 h night time simulated driving task (speed limit 80 km/hr), Saliva, KSS, PPVT, KDT, 30-min break, From 23:55 to 05:30 two times of test battery under one of 3 counterbalanced light treatments including blue light, red light and ambient white light, test battery included KSS, 2 h simulated drive, Saliva, KSS, PPVT, KDT, 30-min break,	A significant effect of light conditions on PPVT reaction times and lapses, Mean reaction time was faster under blue light than ambient light both during ($p = 0.038$) and after light exposure ($p = 0.048$), PPVT lapses increased significantly under all light conditions, No significant difference between red (placebo) and ambient light, No main effect of light conditions on subjective sleepiness, A significant increase in subjective sleepiness in night No main effect of light conditions on driving simulator performance (lateral lane deviations) $F_{2,14} = 17.10$, $p< 0.001$ Lateral lane deviations became progressively worse across the night in

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	performanc e			PPVT (mean reaction times RTs, and the number of lapses (RTs > 500 ms), Lateral lane deviations using a fixed base System Technology Incorporated (STI) simulator	From 5:55 to 8:30 the post-light test battery under ambient white light condition included KSS, 2 h simulated drive, Saliva, KSS, PPVT, KDT, A minimum 4 weeks wash out period between three counterbalanced lighting sessions, Using red light as the Placebo condition with light intensity equated in photopic lux (1.1 lux) to blue light, rather than equal photon density, so the light sources were perceived to be of similar intensity,	all light conditions, A decrease in the SEMs (slow eye movements) by placebo red light as compared to ambient, Significant effect of light condition on theta activity found ($F_{2,12}$ =9.76, p = 0.003). Blue light reduced theta activity. Planned contrast showed that blue light compared to ambient light reduced theta activity both during (p = 0.031) and after light exposure (p = 0.030), No effect of light condition on alpha activity. Alerting effect by blue light via mechanisms other than melatonin since the nocturnal exposure blue light could offset the homeostatic sleep drive induced by sleep loss but did not suppressed melatonin
Cajochen et al. (2000), Between groups design	Compariso n of direct effects of night time exposure to	23 healthy young males (n = 22) and female (n = 1) volunteers	50 h constant routine without sleep to assess core body	Core body temperature, Plasma melatonin, Objective	A 9-day protocol consisting 3 days laboratorial regular sleep-wake time and a 50 h constant routine (awake, semi recumbent under dim light of 10 lux at eye	Dependence of subjective sleepiness (KSS), plasma melatonin and core body temperature on luminance level such that KSS was less deteriorated under 9100 lux and 106 lux than 3 lux,

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	different light intensities (3 – 9100 lux) on human circadian clock objective and subjective measures of alertness during wakefulness	aged 18 – 44 years (mean: 27.8 years)	temperature, one recovery sleep of 8 h, going to bed again starting 4.5 h after their minimum core body temperature (starting between 23:00 and 5:30)	alertness (Karolinska drowsiness test (KDT), Subjective sleepiness (Karolinska sleepiness scale, KSS), EEG alpha and theta activity, Slow eye movements using (SEMs)	level) to assess initial phase of core body temperature, An 8h recovery sleep starting 4.5 h after the CBT minimum (23:00 – 05:30) under 3 lux ambient light levels, participants were randomly exposed to a 6.5 h single illuminance, ranging from 3 to 9100 lux, being cantered 3.5 h before their expected CBT minimum and ending 0.25 h before their expected CBT minimum, A second constant routine of 30 h duration to assess the effects of the experimental light pulse on the circadian phase, Assessment of subjective sleepiness (Karolinska sleepiness scale, KSS), plasma melatonin and objective alertness (Karolinska drowsiness test, KDT) in 30 min, 30 min	A rapid improvement in subjective sleepiness in 9100 lux compared to low intensities, A significantly lower plasma melatonin level under entire 6.5 h exposure to high intensity group than low light levels, A stable level of both alertness and plasma melatonin in both groups exposed to high intensity and low intensity after 2 h exposure, A higher mean core body temperature during exposure to the high intensity light, Mid and high illuminance decreased EEG alpha-theta frequencies (5-9 Hz) in the last 90 min more than low intensities ($P < 0.002$) A steep dose-response relationship between light intensity and subjective alertness, SEMs and EEG theta–alpha activity such that half of maximal alertness in 9100 lux can be induced by 100 lux and SEMs and EEG theta–alpha activity are two times higher in 9100 lux

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
					and 1 h intervals after awakening. respectively, Classification of light intensities into 3 classes: first 33rd percentile (3 lx), second 33rd percentile (106 lx) and third 33rd percentile of the illuminance range (9100 lx).	than those in 180 lux and 90 lux
Okamoto et al. (2014), within participant repeated measures design, day time study	To investigate the effect of long and short-wavelength lights on human alertness in early morning	9 participants (5 men, 4 women) aged between 22 and 34 yrs old	Sleep loss (90 min earlier wake up in the morning) with one week intervals	EEG alpha and theta band power densities	Three times recording EEG with one week intervals, EEG was recorded in 2.5 min periods, in the last 2.5 min of darkness, and 6 times during light conditions (for 2.5 min at 5 min intervals)	No main effect of light condition for EEG alpha and theta was found, The EEG alpha power was lower under both blue and red lights as opposed to placebo (darkness) conditions in the 30, 40 and 50 min after starting the experiment, A main effect of time interval for theta was found with the EEG theta power being larger 30, 50 and 60 min after starting the experiment.
Phipps –Nelson et al. (2003)	To examine the effects	16 healthy adults (10	First 9 days normal sleep,	EEG measures	Participant randomly fixated to either 1000 lx bright light or 5	A significant main effect of light group $F_{1,13} = 6.258$, $p < 0.05$ (attenuated

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
The mixed factorial design, day time study	of daytime bright light as compared with dim light on subjective and objective measures of sleepiness, psychomotor vigilance task and salivary melatonin among partially sleep deprived participants	women, 6 men) aged between 18 and 35 years	On day 10 sleep restriction to 5 hours (from 1 a.m. to 6 a.m.), a constant routine from day 11 afternoon to the end of experiment under dim light. On day 11 sleep from 1 a.m. to 6 a.m. (5 h sleep)	using KDT for 4 minutes, Subjective sleepiness (KSS), Psychomotor vigilance task (auditory PPVT), KDT, PPVT and KSS were calculated as deviation from baseline (baseline values were mean values before light exposure),	lux dim light (from 12.30 p.m. to 5 p.m., every 10 min), On day 12, from 9 a.m. to noon exposure to dim light and hourly measuring of KSS, PPVT, 4 min KDT, saliva, From 12:30 to 5 p.m. one group exposure to bright light every 10 min, one group to dim light and every 30 min recording KSS and PPVT, 4 min KDT, saliva, From 5 p.m. to 9 p.m. exposure to dim light and hourly measuring KSS and PPVT, 4 min KDT, saliva	subjective sleepiness under bright light from 1 p.m. onward, but increased KSS under dim light), A significant main effect of light group on PPVT: $F_{1,13} = 5.014$, $p < 0.05$, bright light reduced mean reaction times but dim light increased mean RTs, reduced the percentage of KDT epochs containing SEMs, Independency of the effects of bright light on sleepiness and performance from suppression of salivary melatonin, Immediate improvement of PPVT performance after the onset of bright light exposure, whereas KSS improved after 1 h exposure, A significant correlation between PPVT performance and subjective sleepiness under bright light (0.38),

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
				Slow eye movement (SEMs), Salivary melatonin,		
Badia et al. (1991), Constant routine,	To examine the effects of both night time and daytime exposure to bright white light (5000 to 10,000 lux at the cornea) on core body temperature, alertness, and	44 male students (18-32 years) in four experimental groups	Total sleep loss for one night (from 24:00 to 9:00)	Body temperature, Computerized battery of performance, EEG spectral power and dominant frequency theta, alpha and beta bands, Objective sleepiness by	After each block the following fixed order of tests was conducted: Temperature, free-time, snack, temperature, first battery of performance, temperature, EEG, MWT, temperature, Assessment of performance by a battery of different computerized tasks including digit recall, logical reasoning, two-letter search, two-column addition, serial addition-subtraction, and a continuous performance task in each block, Performing a maintenance of wakefulness test for 15 min at	**Alternating BL and DL group:** Increase in the log power density of beta, but not power of alpha and theta bands by night time bright light, indicating alerting effect of bright light, A significant increase in log power density of theta across blocks of bright light $F_{2,28} = 5.9$, $p < 0.05$, A similar pattern of EEG differences by daytime alternate condition (control group), however the differences were not significant. Small differences in sleepiness (MWT) during first two blocks of night time continuous bright or dim light, but a rapid decrease in MWT for blocks 3, 4 and 5,

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	performanc e			maintenance of wakefulness test (MWT),	the end of each block	**Both night-time and daytime alternating condition:** Improvement of performance on all tasks by bright light, more significantly on Digit Recall, Two Letter Search, and Serial Add/Sub, Dim light could not offset deterioration of performance over night, An insignificant worsened performance during alternating daytime exposure, **Continuous BL--DL condition:** Insignificant, but similar to night time alternating condition improvements of performance on all tasks during continuous BL--DL condition,
Rüger et al. (2006), Between groups design,	Compariso n of daytime and night time effects of bright light on psychologi	24 healthy males, 12 in daytime experiment (mean age 23.1 ±1.5 yr), 12 in night time	Experiment A (daytime): first test from 6 p.m. till midnight (4 a.m.), second test from 8 p.m. till 4	Physiological variables (heart rate, EEG, core body temperature and salivary cortisol),	**Experiment A (day time):** The first testing battery (testing 1) from 6:00 p.m. on day 0, with hourly measurements 6 min wake-EEG, ECG recording, salivary cortisol concentration, **The second testing (testing 2):** From 8:00 a.m. until midnight.	Similar effect of light on subjective sleepiness (the KSS) and on subjective fatigue (the VAS-F) and energy level for the daytime and night time bright light exposure independently from the time of day. Interaction effect for the factors condition and exposure $F_{1,22} = 16.8$, $p < 0.001$,

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	cal and physiologic al correlates of human sleepiness	experiment (mean age, 21.8 ± 1.9 yr)	a.m. midnight Experiment B (night time exposure): 26 h extended wake from 6 p.m. till 9 a.m. and the second test from 6 pm till 2 am,	Psychologica l variables (the subjective sleepiness KSS), fatigue (visual analogue scale) and energy),	Exposure to bright light or dim light from noon until 4:00 p.m. **Experiment B (night-time exposure):** The first testing battery started at 6:00 p.m. on day 1 and lasted until 9:00 a.m. on day 2 during which the participants were exposed bright light or dim light from midnight until 4:00 a.m. **The second testing**: Lasted from 6 p.m. to 12:00 a.m. of the next day (day 3),	Increased heart rate by night time exposure to bright light $F_{1,11} = 22.9$, $p = 0.001$, and reduced circadian drop in core body temperature by night time bright light, No effect of daytime exposure to bright light on heart rate ($F_{1,11} = 0.2$, $p = 0.604$) and temperature
An et al. (2009), Repeated measures within participant design	To explore the time-of-day-dependent effects of two different wavelength s of light, 458 nm and	12 males (mean age 20.92)	Normal sleep for one week before experiment monitored by Actigraphy, 2 experiments with three dayintervals	Subjective alertness (kwansei gakuin sleepiness scale; Ishihara et al., 1982), Arousal level (Alpha	Monochromatic light exposure for two times (daytime and night time), 12 h out of phase with each other with day time exposure 9 h after awakening, Collection of subjective alertness scores (the kwansei gakuin sleepiness scale) before each session, During monochromatic light	A higher alpha attenuation coefficient (AAC) $F_{1,11} = 10.89$, $p < 0.01$, representing a higher level of arousal at night time than in the daytime, under both 458 nm or 550 nm light, No change of subjective sleepiness between day and night time $F_{3,11} = 0.717$, $p > 0.05$, A considerable interaction among wavelength, time of day, and EEG

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	550 nm, on human higher cognitive function			attenuation test, AAT), Cognitive function (event-related potential, ERP) during an oddball Task, EEG and EOG activity, Visual psychomotor performance task (reaction time, RT)	exposure, performing an alpha attenuation test (AAT) for 6 min, followed by an approximately 20 min oddball task to extract P300 event-related potentials,	electrode site such that, during 458 nm light exposure, participants paid more attention to perform the oddball task at night time than in the daytime, An increased P300 amplitude (higher cognitive function) after 458 nm light exposure more than 550 nm, Dependence of the time-of-day effects of monochromatic light exposure on human cognitive function to light wavelength.
Lockley et al. (2006), Constant routine	Comparison of effects of long-time exposure to 460 nm	16 healthy participants (8 women; mean age = 23.3 ± 2.4 years; range 19-27	A 9-day protocol: a 3-day baseline, an initial 50 h 10-min waking	Core body temperature, plasma cortisol, subjective sleepiness,	Measurement of the KSS was presented every 10 to 20 min for the first 90 min awake, every 30 to 60 min during the 16 h wake episode, including the start light exposure, and every 1 h after	No significant difference in KSS scores, and in performance measures between two groups (460 nm, n = 8; 555 nm, n = 7) at the onset of light exposure, No change in subjective sleepiness among two groups during light

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	monochromatic light with effects of 555 nm monochromatic light on subjective and objective correlates of arousal	years)	constant routine (day 5-6), an 8 h sleep episode without ambient light (day 6-7), a 16 h daytime light exposure without ambient light, an 8-hour sleep episode without ambient light, a 29 h 50 min waking constant routine, and an 8 h sleep episode	Auditory psychomotor vigilance task (PPVT, auditory reaction time, auditory lapses), EEG, EOG, ECG and Karolinska Drowsiness Test (KDT), (PPVT) and Karolinska Drowsiness Test (KDT) hourly throughout the constant-routine and light-exposure	light exposure, Measurement of performance every 30 to 90 min using an auditory 10 min test	exposures for up to a 1 h after exposure ended. However, sleepiness increased in both groups after that time coinciding with the circadian nadir in alertness, Faster auditory reaction times and median reaction times throughout exposure to 460 nm light than during exposure to 555 nm monochromatic light, Reduction in auditory lapses, during exposure to 460 nm (< 4 per 10 min test) as compared with 555 nm light, Improvement of psychomotor performance parameters persisted for up to 1 h before deteriorating at circadian nadir, Reduction of EEG power densities delta-theta and increase in the EEG the EEG alpha power densities during exposure to 460 nm, No significant difference in cortisol levels during exposure to both 460 nm and 555 nm light,

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
			without ambient light. Overall after constant routine there were recovery sleeps,	episode.		
Lafrance et al. (1998), Repeated measures, between participants (two groups)	To examine stimulating effect of bright light on daytime vigilance without suppression of melatonin secretion or without circadian phase shift	14 normal participants (10 women, 4 men; 19 –24 years old)	8 nights normal sleep monitored by Actigraphy, Two nights of 4 h sleep restriction from 4 a.m. to 8 a.m.	Immediate alertness (Visual Analogue Scales), Daytime sleep latencies, PPVT (mean reaction times, percentage of errors), Total number of gaps	Matching the participants for gender, for age and for the mean daytime sleep latency for two groups and administration of two nights of 4 h sleep restriction, Assessment of daytime vigilance before, during, and after the two days of light exposure and sleep restriction, including physiological sleep tendency, subjective alertness, and performance, Assessment of subjective alertness (VAS) every 30 min	A decrease in subjective alertness and daytime sleep latencies significantly by two nights of sleep restriction, No effect of two nights of sleep restriction on performance due to practice effect, A significant day effect only in bright light group on mean reaction time ($p < 0.0001$); decrease of RTs from pre-light day to day 1 of light exposure and day 2 of light exposure ($p < 0.05$), A significant day effect on percentage of errors only in bright light group ($p = 0.01$); increase of percentage of errors from pre-light day to day 1 of light

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
				(reaction times longer than 1 s) during four-choice reaction time test, 4-CH), Salivary melatonin,	throughout all the time awake and every hour during the light exposure, Assessment of the performance by four-choice reaction time test (4-CH) every 2 h in all times except 1.5 h after the end of the light treatment,	exposure and day 2 of light exposure ($p < 0.05$), No improved subjective alertness or increased sleep latencies or global performance by daytime bright light or dim red light, A change in the method of performing PPVT as faster reaction times and increased percentage of errors by bright light, No suppression of melatonin secretion or circadian phase shifts by bright light,
Taillard, et al (2012), Randomized placebo-controlled crossover study	Compariso n of the effects of continuous exposure to monochro matic blue light with coffee or	24 young (20–25 years) and 24 middle-aged (40–50 years) healthy male volunteers excluding night workers	Lateral position (number of inappropriate line crossings ILC), SD of the lateral position of	Blue light (468 nm ± 8 nm), delivered from a light source in the middle of the dashboard (approximate	Three randomized night-time driving sessions for all participants (from 1:00 a.m. to 5:15 a.m.) with more than one weak washout between two sessions, Driving 400 km for 4 h with a 15 min break in the middle of the session, either under	A significant reduction in the number of inappropriate line crossings and SD of the lateral position by both blue light and caffeine, Effectiveness of blue light in short and long driving periods and throughout the night, even at the circadian trough, Nocturnal driving impairment under light exposure and caffeine intake

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	caffeine placebo on actual night-time driving performance	and professional drivers	the car (SDLP in cm), Sleep duration, quality and timing of 3 subsequent sleeps after driving, Sleep efficiency	ly 75 cm from the participant's eyes), Luminance at the eye level 20 lux with an intensity of 7.4 mw/cm^2	continuous blue light during driving or 2*200 mg of coffee or placebo of coffee (15 min before driving and at the beginning of the break), Actigraphy for 3 days after each session to track quality/quantity of sleep and the regularity of the sleep wake cycle.	corresponds to a blood alcohol concentration (BAC) of 0.08%, less than blood alcohol concentration (BAC) of 0.10% under placebo, No effect of age on driving performance, No effect of temporary continuous nocturnal blue light exposure on quantity and timing of subsequent sleep, Eye-related discomfort or visual problems among 17% of drivers,
Hartley, et al (2013), randomized cross-over study	To examine the effects of caffeine and nocturnal bright light on simulated night-time driving in sleep-deprived	12 males aged 20 to 50 years	EEG, Lane drifting (the SD from the central road position), Number of crashes as left lane crossing (number of times centre	White polychromatic light (10,000 lux) at a distance of 30 cm Placebo light (< 50 lux),	Exposure to one of four treatments at the beginning of each session (1 a.m.) with one week wash out between two sessions, **Treatments:** Caffeine (capsules containing 200 mg) plus bright light (C+L+), caffeine plus bright light placebo (C+L—), caffeine placebo plus bright light (C—L+), and caffeine placebo plus	Increased in lane drifting, subjective fatigue and sleepiness (VAS), but decrease in reciprocal reaction time 1:30 a.m. to 4 a.m. and 6 a.m. in the absence of caffeine or bright light (the placebo condition), A decrease in lane drifting, but not immediately by caffeine and bright light (C+L+): the first effect of bright light was a decrease in speed deviation in the 2 h after treatment, The most significant effects of caffeine

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
	individuals		of the vehicle crossed over the edge of the lane or blocked a vehicle passing in the left lane), Speed deviation (the mean sum of differences, km/h, between vehicle speed and posted speed limit) Mean reciprocal reaction time, Number of lapses,		bright light placebo (C—L—), Each testing session included one 30 min treatment following by four 30 min randomized periods of simulated driving or PPVT, The ambulatory polysomnography at home followed by a recovery sleep,	plus bright light (C+L+) as improved lane drifting and reciprocal reaction time at 6 a.m. No change in the quantity and quality of recovery sleep by treatments, A smaller lane drifting by caffeine plus light (C+L+) than placebo caffeine plus placebo light (C—L—), A smaller number of lapses by caffeine plus placebo light (C+L—) than placebo caffeine plus light (C—L+) or than placebo caffeine plus placebo light (C—L—). Therefore, caffeine was more effective in decreasing the number of lapses, Higher effect of caffeine than light on decreasing subjective sleepiness, A worsened mean RRT by caffeine in the absence of light,

Study and design	Aim of study	Sample	Sleep loss status	Outcome measures	Timing of recording of outcomes	Results
			Subjective vigilance (visual analogue scales) Sleepiness and recovery sleep			

4.5 COMPARISON OF ALERTING EFFECTS OF LIGHT AND CAFFEINE

In some studies, the alerting effects of light have been compared with those of caffeine. Table 4.3 represents the methodological analysis of two studies comparing the alerting effects of light and caffeine.

In the first study Taillard et al. (2012) compared the effects of continuous exposure to 20 lux monochromatic blue light (spectral wavelength of 468 nm) with two doses of 200 mg coffee or caffeine placebo on three randomized 4 h night time on-road driving performance tests among young and middle-aged sleep-deprived participants.

In the second study Hartley et al. (2013) used a randomized cross-over design to examine the effects of four interventions including caffeine (capsules containing 200 mg) plus bright white light (10,000 lux), placebo of caffeine (50 mg) plus bright light, caffeine plus bright light and placebo of caffeine plus placebo of bright light (50 lux), on simulated night time driving among sleep-deprived individuals. Each testing session included one 30 min intervention following by four 30 min periods of simulated driving. In both studies there was a one-week washout period between each test session. These two studies revealed the following findings:

In the absence of caffeine or bright light (the placebo condition) lane drifting and subjective vigilance (VAS) increased, but reciprocal reaction time decreased (Hartley et al., 2013).

Blue light (40 lux) or caffeine (200 mg every 2 h) when administered individually could significantly reduce the number of inappropriate line crossings and standard deviation of the lateral position (Taillard et al., 2012). Similar effects were with bright white light (10000 lux) plus caffeine which significantly decreased lane drifting and reciprocal reaction time. Moreover, bright white light on its own decreased variations of speed (Hartley et al., 2013).

Blue light was effective in short and long driving periods and throughout the night, even in the circadian trough (Taillard et al., 2012), while the effects of white light on speed or effects of white light plus caffeine on lane drifting and reciprocal reaction time appeared at least 2 h after receiving light (Hartley et al., 2013).

The magnitude of effects of blue light or caffeine corresponds to a blood alcohol concentration (BAC) of 0.08% which is far less than the BAC of 0.10% under the placebo caffeine (Taillard et al., 2012).

Caffeine was more effective in decreasing the number of lapses and in reducing subjective sleepiness than bright white light (Hartley et al., 2013).

Table 4.3: Methodological analysis of two studies comparing alerting effects of light and caffeine

Author	Sleep-wake schedule	Intervention type	Intervention method	Outcome measures	Limitations/ gaps
Hartley et al. (2013), Night time simulated driving	15 days before starting study and throughout 3-week study (from 9 p.m. to 6 a.m., or from midnight to 9 a.m.)	Counterbalanced receiving treatments: white bright light (10000 lux), or placebo of white light (50 lux), PLUS caffeine (200 mg) or placebo (0 mg)	From 1 a.m. to 1.30 a.m. (30 min) only once-off exposure to treatment, followed by four times 30 min performing first KSS, VAS, and counterbalanced simulated driving or PPVT	**Simulator:** Lane drifting[1], number of crash[2], speed deviation[3] Vigilance (10-min **PPVT):** Mean reciprocal reaction time[4], number of lapses[5], visual analogue scale (VAS) score, Karolinska sleepiness score (KSS), 24 h EEG (four channel), EOG, ECG, EMG recording during all the study day and during 3 consecutive recovery sleeps.	No study of daytime exposure to light, No chronic partial sleep loss, No specific study of blue or red light in low levels, Measurement of outcomes only after finishing treatments not during exposure to light, Short time exposure to light (30 min), Using high dose (200 mg) of caffeine,
Taillard, et al (2012), Night time on-road driving	Sleep from midnight ± 2 h to 8 a.m. ± 2 h one week prior and during one-week washout	Participants received counterbalanced either continues blue light (468 nm, 20 lux) or 2* 200 mg caffeine or placebo (15 mg) before driving and during break	From 1 am to 5:15 a.m. 4 h with 15 min break in the middle of on-road driving session	The number of inappropriate line crossings (ILC)[6], Lateral Position[7], SD of the lateral position	No study of daytime exposure to light, No chronic partial sleep loss, Using high dose (2*200 mg) of caffeine, Limitation of outcome measures to in-vehicle outcomes without EEG and cognitive performance,

1-Lane drifting: standard deviation from the middle of the road,

2- Number of crash: frequency of crossing the centre of vehicle to the left or the right lane,

3-Speed deviation: mean sum of differences between speed and posted speed limit,

4- Mean reciprocal reaction time: 1/mean reaction time in seconds,

5-Number of lapses: number of reaction times more than 500 milliseconds,

6- An ILC was recorded when the car crossed a right or left lateral lane, whatever the duration and the amplitude of the crossing,

7- Lateral position was defined as being 0 when the car was in the centre of the lane, with positive values to the right and negative values to the left

4.6 SUMMARY AND IMPLICATIONS

The literature review was conducted with the purpose of understanding the alerting effects of light and caffeine on driver alertness and performance and determining the types and doses of light and caffeine needed for the experimental study.

Low doses of caffeine, less than 100 mg, were found to improve driving performance outcome measures. Caffeine in the form of gum was found to have a very high absorption rate. Therefore, a low dose of caffeine, preferably chewing gum, seemed suitable for the experimental study to address the alerting effects of minimum but routinely consumed caffeine by young drivers.

Studies of alerting effects of light on sleepy drivers via both night time and daytime protocols have highlighted some conflicts about the positive effects of light on objective, subjective and performance outcomes of driver sleepiness. These discrepancies raised from differences in protocols utilized, physical characteristics of light (intensity, wavelength, pulse or continuous light), the timing of exposure, duration of exposure, sensitivity of outcome measures to light, inter-individual differences (age, gender, intolerance to bright light) and so on.

Generally, night time studies suggest that some indices of alertness such as subjective sleepiness and EEG theta–alpha activity have a dose-response relationship with light, such that even ambient room light can enhance both objective and subjective alertness (Cajochen, C., 2007). EEG correlates of alertness appear to be more sensitive to light than behavioural measures of alertness (Figueiro, M.G et al., 2009). Some of studies have found that shorter wavelengths of light (blue range) have more stimulating effects in the visible spectrum requiring lower intensities to elicit their alerting effects (An et al., 2009), such that blue light seems to elicit a greater decrease in waking EEG power density in the delta-theta frequency range (sleep related range), greater increase in power density in the alpha range (relaxed wake), and greater enhancement of auditory performance (Lockley et al., 2006), particularly in reaction times and driver performance (Taillard et al., 2012).

Daytime experiments revealed that bright light elicits some improvements in objective and subjective alertness measures, such as decreased eyes-open EEG alpha activity (Badia et al., 1991; Kaida et al., $2006_{(b)}$), attenuated subjective sleepiness

(Leger et al., 2009; Phipps-Nelson et al., 2003; Smolders et al., 2012), and improved psychomotor performance test (PPVT) (Phipps-Nelson et al., 2003).

Based on these findings there was a need for taking a multidimensional approach to measure the alerting effects of light and caffeine to ensure that these stimulants elicit some alerting effect on subjective outcomes and induce a false sense of security among drivers but not improve driver performance outcomes to a considerable extent. Therefore, relying on one level of alertness to examine the alerting effects of light or caffeine would not be beneficial.

4.7 GAPS IN THE EXISTING KNOWLEDGE

This literature review revealed some important gaps in our current knowledge of the effects of light and caffeine on driver alertness and performance as follows:

a. An alerting response to light appears to be a robust finding in laboratory studies, mostly observed after acute total or partial sleep loss, but little is known about alerting properties of light under chronic sleep loss.

b. It is not still clear that how light can fit in the current computational models of sleep-wake or alertness regulation, because these models do not incorporate light as an input.

c. The important light properties (e.g. optimum intensity, wavelength, and duration) to exert alerting effects are not known.

d. The effectiveness of light in terms of sleep homeostatic and circadian factors is largely unknown.

e. The effects of light on daytime human alertness and performance is not well understood, since most studies have been undertaken during night time to maximize decline in performance and alertness through coincidence of circadian and homeostatic drives for sleepiness.

f. The studies of light and caffeine did not show a consensus on the washout period of light or caffeine in the driving context. Regarding light, minimum adaptation to darkness appeared to be necessary. For caffeine, maximum time was needed for measuring the alerting effect of caffeine.

g. The literature supports the possibility of caffeine and light as countermeasures for sleepiness. However, the relative alerting effects of each as well as the effects of light and caffeine in combination on sleepiness outcomes have not been examined.

Taking above-mentioned gaps in our knowledge into consideration, there was a need to adopt a chronic partial sleep loss paradigm to compare the effects of light and caffeine on objective, subjective and performance measures of sleepiness among young drivers. An experimental study was conducted to explore the possibility of light as a countermeasure for sleepiness either alone or combined with caffeine. Obviously, all existing gaps could not be addressed by one study. Therefore, some pragmatic approaches were considered to specifically bridge some of above-mentioned gaps. A summary of existing gaps in the knowledge of alerting effects of light and caffeine, as well as the approach taken to bridge those gaps are provided in Table 4.4.

Table 4.4 Existing gaps in the effect of light and caffeine on drivers' alertness and performance

Gap in the knowledge	Approach to address the gap
Most studies of alerting effects of light are based on acute total or acute partial sleep loss, not on chronic sleep loss,	Adopt a chronic partial sleep loss paradigm,
The effects of light in daytime on driver alertness is not well understood, since most of studies have been undertaken during night time to maximize driver's sleepiness,	Running the experiment during daytime,
The nature of effects of light on driver alertness is not known,	Utilizing broader ranges of outcome measures of sleepiness including objective, subjective and driver's driving performance,
The magnitude of alerting effects of light compared to current countermeasures such as caffeine alone has not been determined,	Comparison of effects of light with those of caffeine by adopting a factorial design,
Washout periods of light and caffeine are not known ,	Administration of dark adaptation before experiment to eliminate any potential remaining alerting effects of light, setting a maximum time for measuring the effects of caffeine.

Chapter 5: Experimental Study

This chapter describes the major experimental study conducted to address the aims and objectives stated in Section 1.3 of Chapter 1. Section 5.1 discusses the methodology used in the experimental study and the research design. Section 5.2 details the participants and the study's inclusion and exclusion criteria and sample size justification. Section 5.3 includes the list of all the instruments and the outcome measures used in the study. Section 5.4 describes the interventions adopted in this study. Section 5.5 outlines the procedure of the study from recruitment to test session. Section 5.6 discusses how the data was processed before explaining the analysis of data in Section 5.7. Finally, Section 5.8 discusses ethical and technical considerations raised by the study.

5.1 METHODOLOGY AND RESEARCH DESIGN

5.1.1 **Methodology**

This study was a laboratory-based quantitative experiment. This approach was intended to compare the effects of light, caffeine and light and caffeine in combination on drivers' performance when sleepy.

5.1.2 **Research Design**

The experimental study adopted a within-participant repeated measures factorial design. The independent variables comprised two levels of the *Light Condition* (blue-green light and Placebo (red) light) and two levels of a *Caffeine Condition* (Caffeinated gum and Placebo (decaffeinated) gum).

The interventional conditions presenting either caffeinated gum (Active Caffeine) or placebo non-caffeinated gum, in conjunction with either blue-green light (Active Light) or red light are presented in Table 5.1.

The four interventional conditions that were presented in a partial-counterbalanced order across three test sessions. Condition 4 (Placebo caffeine and placebo light) was presented first on each test session.

Table 5.1 The interventional conditions

	Active Light	Placebo Light
Active Caffeine	1	3
Placebo Caffeine	2	4

In this thesis the above mentioned four interventional conditions are referred to as follows:

Condition 1 (Active light plus Active Caffeine): Light and caffeine in combination,

Condition 2 (Active Light plus Placebo Caffeine): Light alone,

Condition 3 (Placebo Light plus Active Caffeine): Caffeine alone,

Condition 4 (Placebo Light plus Placebo Caffeine): Placebo condition

The Active Light was 500 nm dominant wavelength UV-free light (perceptually blue-green) with an illuminance of 506 Lux (lm/m²) and irradiance of 230 (µW/cm²). The Placebo light was created by using the same emitter, but covering the LEDs with a Wratten neutral density red filter (SHEET 0.3ND)**.** These filters specifically absorb blue-green light (Onley & Boynton, 1962) and provide a perceptually very dim red light output. This Placebo condition was intended to replicate all other aspects associated with wearing the Re-Timer glasses. The Placebo light was not intended to match the Active light in photon density or in spectral profile. While intensity-matched long-wavelength (red) light may have some physiological impacts (Figueiro, M.G et al., 2009), these impacts have not been demonstrated at this low level of illuminance.

Due to the uncertainty in the washout period for caffeine (anywhere from 12 h (Brunyé et al., 2010) to 3 days (Giles et al., 2012), the conditions were partially counterbalanced using a Latin Squares sequence. Specifically, all participants were first exposed to Condition 4 (Placebo Light & Placebo Caffeine condition) then received one of other conditions (1, 2 and 3) in each test session. Each participant received every condition across the three test days. Therefore, there were six potential different condition sequences for each participant across three test days: 123, 231, 312, 213, 321, and 132.

The presentation of Condition 4 at the start of each test before administration of the other counterbalanced active conditions had three advantages:

1. Receiving the placebo condition eliminated the need for including a washout period between the three test days.
2. It reduced the overall time required for accomplishing the study.
3. This approach accommodated day-to-day variations in alertness (Cajochen, C., 2007; Lenné, M. G et al., 1997) by effectively providing daily baselines.

5.2 PARTICIPANTS

5.2.1 **Inclusion criteria**

In order to promote homogeneity in the participant group and to control for factors that might impact on either the independent variable (sleepiness manipulation) or on the dependent measures, some inclusion criteria were defined. Participants were required to meet the following criteria:

1. Be capable of consent,
2. Hold a driving license, with no physical restrictions to drive,
3. Be young adults (age range of 18-25 years). This age group is known to be sensitive to sleepiness (Smith, S. et al., $2009_{(b)}$). Selection of this age group was based on conventional classification of young adults in sleep and circadian studies (Smith, S. et al., $2009_{(a);}$ Smith, S. et al., $2009_{(b)}$),

4. Have self-reported normal vision or a corrected to normal vision (normal vision while using spectacles and or contact lenses).

5.2.2 **Exclusion criteria**

Exclusion criteria were intended to minimize potential confounding factors as previously discussed in Section 2.5. Visual criteria, based on participant self-reported eye diseases, their colour vision and corrected vision, ensured participants could see computerized tests properly, and could distinguish blue light from red light. Potential participants reporting the following conditions were excluded (Table 5.2).

Table 5.2 Exclusion criteria

Exclusion criterion	Description
Sleep disruption	Professional long-haul transport drivers, shift workers, and passengers traveling to different time zones during the past,
Excessive daytime sleepiness	Score greater than 10 as sleepiness was measured by Epworth sleepiness scale (Boyle et al., 2008; Hartley et al., 2013; Johns, M, 1991; Wijesuriya et al., 2007),
Evening Chrono type	Participants who normally go to sleep after 12 p.m. and score less than 30 on the Horne-Ostberg Morningness–Eveningness Questionnaire (Horne, J.A & Ostberg, 1976). Studies have found that the extreme evening types have less exposure to daylight and are more sensitive to sleep loss than are intermediate/morning types (Martin, J. S., Hebert, Ledoux, Gaudreault, & Laberge, 2012),
Significant health problems	Scores above 20 on the Lifestyle Appraisal Questionnaire (LAQ) (Craig & Hancock, 1996),
Acute illness or active confounding medical conditions	Neurological diseases such as dementia, cardiovascular diseases (since cardiovascular diseases may change the heart rate variability), major psychiatric (mental) diseases that may be associated with reduced heart rate variability, vestibular diseases (balance problems)
Large body mass index	Body mass index more than 30 kg/m^2 (Smith, M. R. et al., 2008),
Alcohol use	Habitual consumption of more than 2 standard alcoholic drinks per day (a standard drink contains 10 grams of

Exclusion criterion	Description
	alcohol),
Illicit drug use	Habitual use of opiates (Naturally extracted or semi synthetic drugs) such as opium, morphine, codeine and heroin, opioids (wholly synthetic products) such as methadone, pethidine and fentanyl, sedative-hypnotics such as Methaqualone (Dassanayake, Michie, Carter, & Jones, 2011), Stimulants such as cocaine hydrochloride and crack cocaine, amphetamine and amphetamine-type stimulants (ATS), MDA (3,4-methylenedioxy-amphetamine) and MDMA (3,4-methylenedioxy-methamphetaime or ecstasy), and cannabis; Marijuana and Hashish (Penning, Veldstra, Daamen, Olivier, & Verster, 2010),
Prescription medication use	Current use of beta blockers, melatonin, or melatonin agonists (Hartley et al., 2013), because of direct effects of these medications on sleep, Psychoactive medications. These medications might change the heart rate variability and include: Cocaine for treatment of narcolepsy (Penning et al., 2010), Antihistamines (Engeland, Skurtveit, & Mørland, 2007; Meltzer, 1990), Antidepressants (Dassanayake et al., 2011), Anxiolytics, anticonvulsants such as barbiturates, non-barbiturate depressants (methaqualome) and benzodiazepines (diazepam or Valium) in the treatment of tension and anxiety, insomnia and some psychiatric illnesses (Dassanayake et al., 2011),

Exclusion criterion	Description
Being a caffeine avoider, sensitive to caffeine or a heavy caffeine user	Participants were required to be a normal caffeine user. Caffeine avoiders would feel uncomfortable after caffeine administration during the study. The relatively low levels of caffeine in this study (100 mg) may under-dose heavy caffeine users (consumers of two or more cups of coffee or an equivalent amount of other caffeinated beverages daily). Furthermore, heavy caffeine users might not easily cope with the caffeine curfew prior this study and experience withdrawal effects (Juliano & Griffiths, 2004; Rogers, P., 2014),
Eye and optic nerve diseases	Suffering from retinopathy (Hartley et al., 2013), incompatible colour vision with the driving act (Otmani et al., 2005), or diseases of the optic nerve, or ocular media (Figueiro, M. G., Rea, & Bullough, 2006),
Photosensitivity	Being sensitive to light or having epilepsy. Light has the potential to produce some side effects such as eye strain, headache, and nausea. Eye-related discomfort and/or visual problems among 17% of drivers have been already observed in an on-road blue light study (Taillard et al., 2012).

5.2.3 **Sample size justification**

According to the findings of the systematic review in Chapter 3: most studies of driving performance have adopted quasi-experimental designs with the number of participants in the range of 8 to 50 (Table 3.4). To estimate the minimum sample size for the current study, the primary dependent variable of lane crossing and Cohen's conventions (Cohen, 1992) for relative effect size were adopted (e.g. an effect size represented by Cohen's D of 0.2 to 0.3 might be a "small" effect, around 0.5 a "medium" effect, and 0.8 to infinity, a "large" effect). The systematic review in Chapter 3 showed that the effect size for these performance outcomes has been reported in just one study (Rupp et al., 2004), with a large effect size (0.98) for lane crossing under moderate to severe sleep loss. However, this effect size may be optimistic (in the context of no later replication) and a smaller potential effect size under conditions of mild sleepiness has been assumed. Using statistical software (Swanson & Holton) for repeated measures MANOVA, and within-factors tests and considering statistical power of 0.85, six repeated measurements for lane crossing (overall 6 conditions), an expected 'small' size of the effect of sleepiness on lane crossing (Cohen's D of 0.3), and an alpha level of 0.05, a minimum sample size of 26 participants was estimated. Since all subjects were randomly assigned to one of three counterbalanced interventional conditions (1-3) in each test session, and there were six different orders of presentation for these three conditions, the sample size needed to be a multiple of 6 to secure the equal possibility for each subject to be assigned to one of these six orders of presentations. Therefore, a minimum sample size of 30 participants was determined to meet all requirements.

5.3 MEASURES

Instruments utilised in this study have been classified in two groups: those to assess eligibility of participants and those used for presenting the exposure and measuring the outcomes.

5.3.1 **Instruments for assessing eligibility of participants**

Phone screening questionnaire

A phone call screening questionnaire was developed as the first screening tool on the phone. This questionnaire comprised some questions on inclusion criteria (age, driving licence status and the exclusion criteria (Section 5.2.1). A sample phone call screening questionnaire is provided in Appendix A.

Screening checklist

A screening checklist was designed to assess the eligibility of the participants using responses to the questions asked during the phone call screening and the results of three above-mentioned questionnaires. A sample screening checklist is provided in Appendix B.

Lifestyle Appraisal Questionnaire (LAQ)

Health status was assessed by the Lifestyle Appraisal Questionnaire (LAQ; Craig & Hancock). This is a multi-factorial questionnaire for assessing health status, including items that assess the body mass index (BMI), alcohol intake, prescribed medications, cigarette intake, exercise, social support and so on. Scores above 20 on the LAQ suggest lower health status, which increases sleepiness risk (Craig & Hancock, 1996; Wijesuriya et al., 2007). This questionnaire is provided in Appendix C.

Horne-Ostberg Morningness– Eveningness Questionnaire (MEQ)

Individual chronotype was assessed by the Horne-Ostberg Morningness–Eveningness Questionnaire (MEQ; Horne, J. & Ostberg; Horne, J.A & Ostberg, 1976). This questionnaire indicates whether the individual's peak sleepiness falls during the morning, evening, or at an intermediate time of day. The MEQ consists of 19 multiple-choice questions and four response options for each question, representing the *preference* of the respondent for sleep/wake time rather than their actual sleep/wake time. The sum of scores ranges from 16 to 86; scores of 41 and below represent "evening types", with extreme evening types scoring less than 30.

Scores from 42 to 58 indicate "intermediate types. Scores of 59 and above indicate "morning types", with extreme morning types scoring more than 70 (Horne, J. & Ostberg, 1975). This questionnaire is presented in Appendix D.

The Epworth Sleepiness Scale (ESS)

Excessive daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS; Johns, M, 1991). This scale, although intended as a measure of sleep propensity, has been widely used as a general measure of daytime sleepiness. The ESS comprises eight items reflecting the individual's potential for falling asleep in different situations such as sitting and reading, sitting while talking to somebody, in a car, or while stopping in traffic. The score for each item varies from 0 = 'never would doze' to 3 = 'high chance of dozing'. Each subject scores between 0-24. The ESS has showed a high test-retest reliability ($r = 0.82$, $p < 0.001$), and satisfactory internal consistency (Cronbach's alpha = 0.88) among people with various sleep disorders (Johns, 1992). The validity of ESS is questionable, since it has shown associations with objective measures of sleepiness, such as the Multiple Sleep Latency test (MSLT) that range from moderate (Johns, M, 1991) to insignificant (Fong, Ho, & Wing, 2005). A sample ESS is presented in Appendix E.

Pittsburgh Sleep Quality Index

Sleep quality was assessed by the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer), a self-rated questionnaire to assess sleep quality and disturbances over a 1-month time interval. The questionnaire consists of 19 self-rated questions which yield seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score which has a range of 0-21. Any Score greater than 5 represents poor sleep qualities (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002). The PSQI has been used both in psychiatric clinical practice and research activities (Philip et al., $2005_{(b)}$). Backhaus (Backhaus et al., 2002), found a correlation ($r = 0.86$, $p < 0.001$) between test and retest sessions. A sample PSQI is provided in Appendix F.

5.3.2 **Instruments for measuring the outcomes**

Compumedics Somté devices

EEG and ECG activities were recorded by Compumedics Somté (V1) PSG devices (clinical laboratory quality polysomnography; PSG). These devices comprise a data recorder (to record EEG and ECG) and an electrode input box. The data recorder and patient input box are exhibited in Figure 5.1.

Figure 5.1. Compumedics Somté devices for recording EEG and ECG activities, the data recorder is on the left and the patient input box on the right.

The recordings of brain activities were undertaken by placement of EEG and ECG electrodes according to the International 10–20 System of Electrode Positioning. In this method the EEG electrode are positioned in places determined by measurements

from landmarks on the head (Yueh Cheng & Te Hsu, 2011). Measurements were made from left to right at 10-20% of distance from inion to nasion (Harner & Sannit, 1974). A schematic placement of EEG electrodes is provided in Figure 5.2.

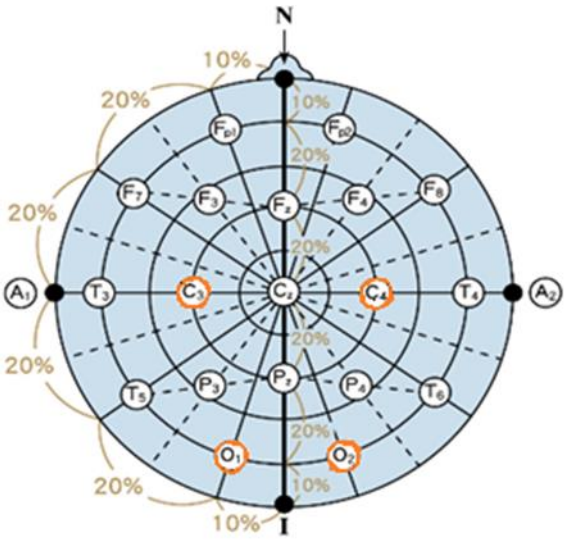

Figure 5.2. International 10–20 system of EEG electrode placement, Fp1, Fp2: prefrontal, F3, F4: frontal, C3, C4: central, P3, P4: parietal, O1, O2: occipital, F7, F8: anterior temporal, N: Nasion, I: Inion, T3, T4: mid-temporal, T5, T6: posterior temporal, A1, A2: ear (or mastoid), Fz: frontal midline, Cz: central vertex, Pz: parietal midline, (z = zero), adopted from (Yueh Cheng & Te Hsu, 2011). The red circles show positions of recording electrodes.

EEG was recorded in all frequencies using gold cup electrodes (Compumedics, 180 cm, 1.5 mm touch proof, 7000- 0044-00). EEG activity was recorded at a frequency of 256 HZ by placement of two electrodes at the central (C4), and occipital (O1) areas and two electrodes behind the ears as reference points (Figure 5.3).

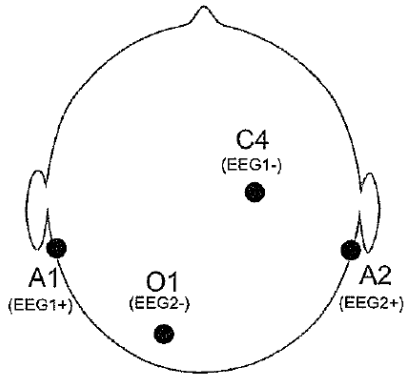

Figure 5.3. EEG electrode placement (adopted from Somté PSG user guide).

ECG was recorded using two Snap-On electrode wires (Compumedics, 180 cm, 1.5 mm touch-proof, 7003-0001-00) attached over the clavicle on the right side and between 5^{th} and 6^{th} rib on the left side (Figure 5.4). In order to test for adequate impedance of all electrodes (less than 5 KΩ determined via UFI 'Checktrode' 1089 MKIII) a ground reference electrode was attached under the left clavicle. After testing for impedance, all electrodes were connected to the corresponding leads in the patient input inbox (Figure 5.5).

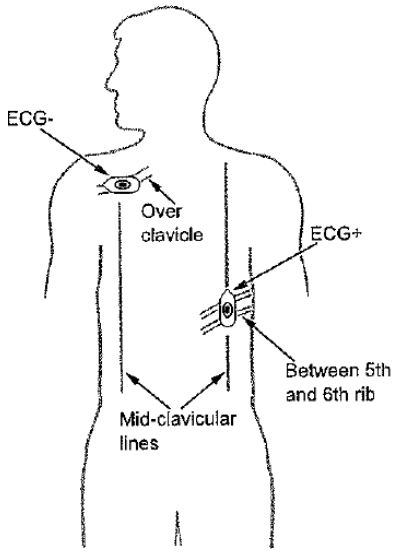

Figure 5.4. Placement of ECG electrodes (adopted from Somté PSG user guide).

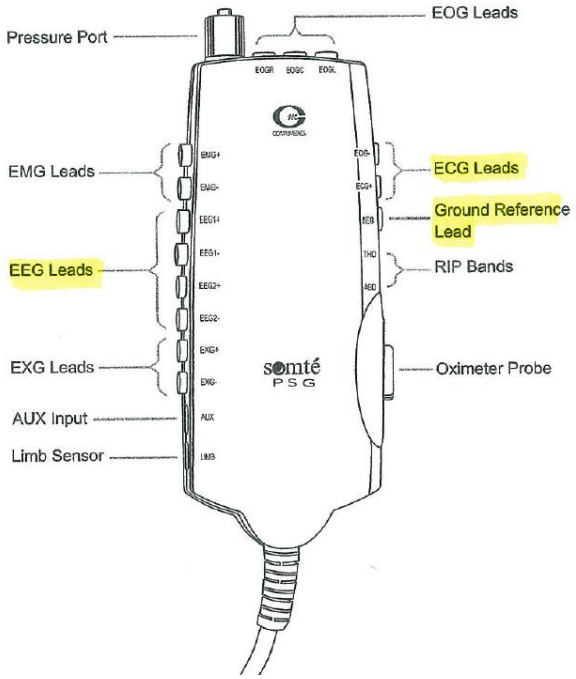

Figure 5.5. EEG, ECG and ground reference leads in Patient Input Box (adopted from Somté PSG user guide).

PEBL Psychomotor Vigilance Task (PPVT)

A specific aspect of the participant's cognitive performance was assessed with a short computerized version (5-min) of the Psychology Experiment Building Language (PEBL) Psychomotor Vigilance Task (PPVT). The psychomotor vigilance task (PVT) is a standard probe widely used in sleep research (Dinges et al., 1997). The PPVT is a simple visual reaction time task in which a circle stimulus appears on a screen at intervals varying between 2 and 12 seconds (Figure 5.6). The participant must depress the spacebar as quickly as possible in response to the stimuli. This task has been found to be free of aptitude and learning effects, and is reliably sensitive to performance variations due to partial sleep loss and circadian rhythm (Cluydts et al., 2002; Jackson et al., 2013; Lim & Dinges, 2008; Ting et al., 2008; Van Dongen & Dinges, 2005).

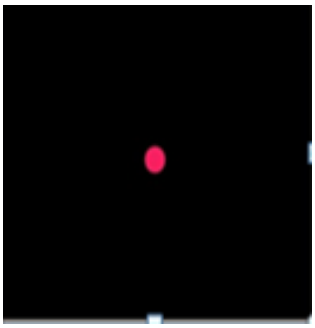

Figure 5.6. PEBL psychomotor vigilance test (PPVT).

The STISIM Drive simulator

In this study a desk-top based driving simulator, STISIM Drive® (Systems Technology Inc. Model 100 Kit), was utilised to simulate the driving scenarios. The STISIM Drive simulator has been widely used in psychophysiological research (over 1,000 studies identified in Google Scholar), including studies of sleepiness and vigilance in healthy subjects (Pizza et al., 2004).

This simulator is capable of sampling up to 40 variables in one driving session. This system comprises a computer system (keyboard, mouse, monitor and a computer), sound system, roadway display device (32" high resolution and colour-calibrated LCD display) and force-feedback wheel and pedal set (Logitech G27). The scenarios are developed in a proprietary scripting language (STISIM Scenario Definition Language). Configuration files define different aspects of the simulation such as the nature of the roadway sections, driver cabin, sound effects, crash effects, and driver view parameters, etc. During a simulation run, the simulator combines predefined settings (configurations) and programs (scenario events) to create a desired graphic in each visual frame in response to driver control of the virtual car using the steering wheel, gas, and brake pedals. These data are processed in the simulation kernel and run to the end of the simulation. The mechanism of simulation is provided in Figure 5.7.

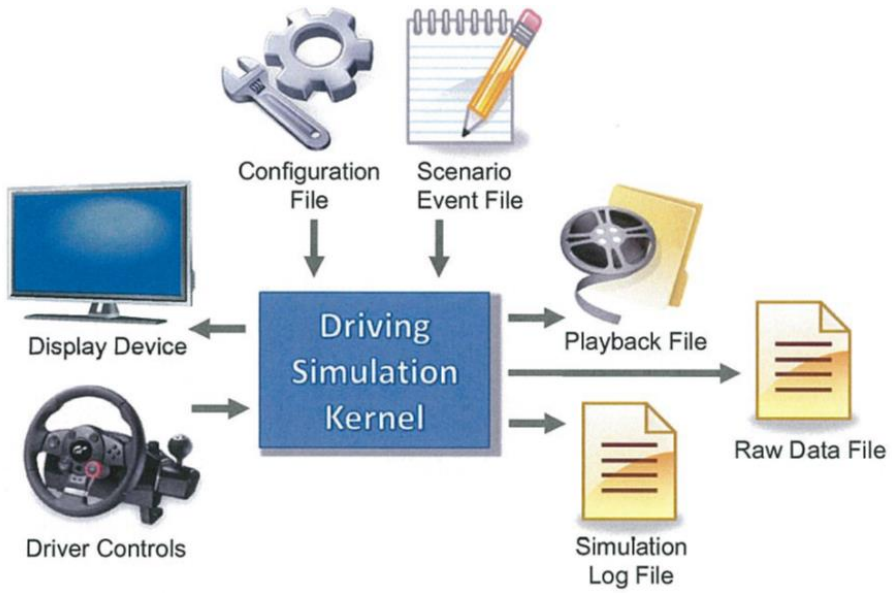

Figure 5.7. Mechanism of simulation by the STISIM Drive simulator, adopted from STISIM Drive Getting Started manual.

Figure 5.8 represents a basic road way scene shown in a single simulation visual frame. The different road way sections (width of lanes, shoulders, fore slopes, etc.) are defined in a scenario event file and some features of those sections are configured in the configuration file (e.g. colour, texture, side of the road to drive, etc.). This platform allows the researchers to add unlimited elements such as vehicles, road signs and billboards, hills, buildings, bridges, rivers, and intersections to develop the scenario to meet the experiment demands.

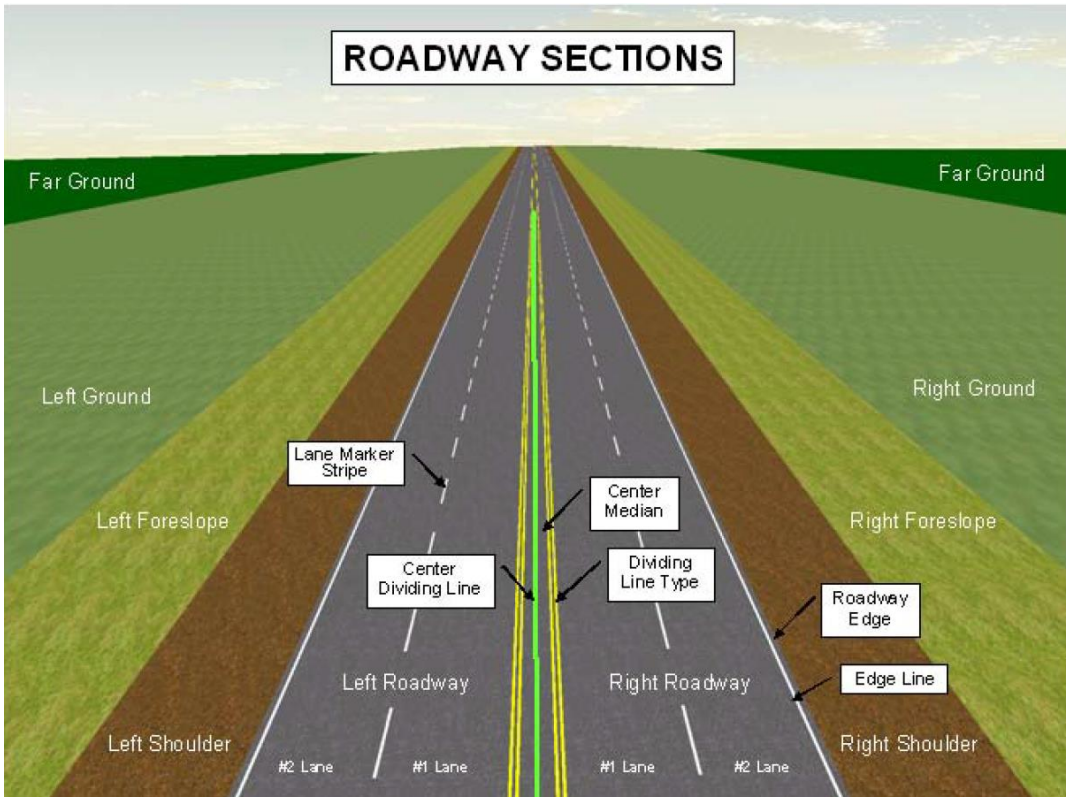

Figure 5.8. Basic road way sections simulated by the STISIM Drive simulator, adopted from STISIM Drive Scenario Definition Language Events manuals.

Three new driving scenario projects were developed for this study. The scenarios had identical physical structure (e.g. the distribution and dimensions of straights and curves in the roadway), but each had different roadway backgrounds (appearance of terrain, scenery, etc.). For this purpose, three different configuration and scenario event files were developed. The simulator measurement unit was set in Metric units. The roadway was a 50-km long four-lane rural roadway, two lanes on the left side (ongoing traffic) and two lanes on the right side (upcoming traffic) with defined median, centre line stripes, left edge and right lane markers, left and right edge lines, left and right shoulders, fore slopes and ground areas. The task was intended to replicate a monotonous drive on the road with mostly straight sections and some limited curves, residential areas, and gas stations on both sides of the road and a city area at the end of the drive. To reduce potentially alerting feedback, the crash visual effects, off-road sound effects, and traffic violation sound effects (violation of speed limit) were disabled. The speed limit on the straight sections of roadway was mostly 110 km/h, while there were lower speed limits on the curves and in residential areas

(villages or city) at 80 and 60 km/h, respectively. Considering these speed limits the drive time was 30 minutes, a period intended to be long enough to be sensitive to sleepiness, but not so long as to induce time-on-task fatigue. The driving scenarios were counterbalanced across test sessions to eliminate the practice effect. At the beginning of the drive, participants found themselves on the left side of the roadway and were instructed to drive only on the left side for the entire drive (the standard in Australia). There were some cars and motorcycles on the right lane of ongoing traffic (driver's side), but since drivers were driving on the left lane there was no need to overtake any vehicle. This strategy eliminated the lane deviation data from overtaking other cars. Additionally, in each test day in order to minimize the learning effect from first drives on the second drive on the same scenario, the random selection of immobile and mobile cars, pedestrians and buildings was included in the of scenario. Therefore, drivers could not remember the exact sequence of events in the second play of the same scenario. There were also no obstacles in the road, no cars pulling out onto the road, and no pedestrians or animals unexpectedly crossing the road. In addition to minimising learning effect, these features were intended to minimize the possibility of deviations in lane position of the car or large steering wheel movements while overtaking other cars or sudden reactions to an unexpected event. On the occurrence of collisions, the simulator did not stop and continued displaying roadway objects after the crash and did not reset speed or position of the car. A frame of simulated roadway is represented in Figure 5.9.

Figure 5.9. A frame of simulated roadway by the STISIM Drive simulator as viewed by the participant

The simulation image refresh rate for this study was set to 120 frames per second, resulting in a perceptually continuous and uninterrupted roadway scene. The simulator was set to sample the variables with a sampling frequency of 60 Hz. This means that the simulator sampled those variables repeatedly once every 0.016 seconds. In order to enable the simulator to sample the desired variables, some data saving blocks (epochs) of 4 seconds were defined (Matthews et al., $2012_{(b)}$). Considering the maximum speed limit of 110 km/h, these blocks 4-second blocks were approximately equivalent to 125 m of the roadway.

5.3.3 **Outcome measures**

The dependent variables were comprised of a focussed set of outcome measures intended to assess the three primary constructs of interest; objective sleepiness, subjective sleepiness, and driving performance. Table 5.3 provides the outcome measures for each construct and their definitions in more detail.

It should be noted that since driving performance was a key outcome it was important to understand sensitivity of specific indices of driving performance to the interventional conditions. Therefore, a broad range of relevant driving performance indices (25 variables) were sampled and primarily analysed. These variables were

measuring different aspects of driving tasks including velocity, acceleration, steering wheel angle, lateral lane position, minimum time to collision with other vehicles and pedestrians, minimum range of collision with other vehicles and pedestrians, road crashes with other vehicles and pedestrians, and variables related to line crossing including off road accidents, road edge excursion (inappropriate line crossing) and centreline crossing. Based on the findings of the three literature reviews of sleepiness, effects of sleep loss on young drivers and effects of light/caffeine, some sampled outcome measures (including driving performance outcomes) were selected as primary outcome measures of interest and were analysed further. These primary outcome measures of interest are shown in Table 5.4, followed by a brief rationale for selecting these outcome measures.

Table 5.3: The sleepiness outcome measures in the experimental study

Construct	Outcome measure	Definition
Objective alertness: EEG	Mean Alpha	Mean EEG absolute power (millivolts squared, mV^2) in alpha range (α; 8–13 Hz)
	SD Alpha	Standard deviation of EEG absolute power (Volts-squared per Hz, V^2/Hz) in alpha range (α; 8–13 Hz)
	Mean Theta	Mean EEG absolute power (Volts-squared per Hz, V^2/Hz) in theta range (θ; 4– 8 Hz)
	SD Theta	Standard deviation of EEG absolute power (Volts-squared per Hz, V^2/Hz) in theta range (θ; 4– 8 Hz)
Objective alertness: ECG	Mean RR	Mean beat-to-beat (R-wave peak to R-wave peak) interval
	SD RR	Standard deviation of the beat-to-beat interval
	Mean HR	Mean heart rate
	SD HR	Standard deviation of heart rate

Construct	Outcome measure	Definition
	LF (0.04-0.15)	High-frequency heart rate variability (0.15 to 0.40 Hz)
	HF (0.15-0.4)	Low-frequency heart rate variability (0.04 to 0.15 Hz)
	LF/HF	The proportion of HF (0.15-0.4) to LF(0.04-0.15) heart rate variability
Objective alertness:	Lapse frequency	Number of responses longer than 500 milliseconds
PPVT-related outcomes	Mean RT calculated only from correct responses	Mean Reaction Time (interval between stimulus onset and key pressure)
	RT variability calculated only from correct responses	The standard deviation (SD) of the intra-individual RT
	Percentage of false response	Percentage of false response; (number of false responses*100)/total trials
	Percentage of lapses	The percentage of response times greater than or equal to 500 milliseconds for all trials (i.e. lapse %); (number of lapses*100)/total trials

Construct	Outcome measure	Definition
	Percentage of correct responses	The number of times the participant responded to the stimulus by clicking the right key based the dominant hand used for the measure (number of correct responses*100)/total trials
	Mean of the fastest 10% of 1/RT(1/S)	The mean of the reciprocal of the fastest 10% 1/RT (seconds-1) for those who had a correct response to the stimulus. 1000*(mean (reciprocals of top 10% of the fastest response);
	Mean of the slowest 10% of 1/RT(1/S)	The mean of the reciprocal of the slowest 10% 1/RT (seconds-1) for those who had a correct response to the stimulus. 1000*(mean (reciprocals of top 10% of the slowest response)):
	Mean reciprocal correct responses	The mean of the reciprocals of correct responses (not false, not laps)
	Mean reciprocal laps	The mean of the reciprocals of responses longer than 500 milliseconds
	Mean reciprocal correct and laps	The mean of the reciprocals of correct responses and lapses

Construct	Outcome measure	Definition
Subjective alertness	Self-reported sleepiness scores	Sleepiness scores from 1 to 9 on Karolinska Sleepiness Scale (KSS)
Driving performance	Longitudinal velocity	Longitudinal velocity of the driven vehicle or longitudinal speed (metres/second)
	Lateral velocity	Lateral velocity of the driven vehicle (metres/second)
	Mean Lateral Lane Position	Mean Lateral Lane Position of the driven vehicle with respect to the roadway dividing line, positive to the right.
	Longitudinal Acceleration due to the Brakes	Longitudinal acceleration is the total acceleration due to throttle, braking and drag (lateral acceleration). The throttle activity refers to forward acceleration per second (NCSU Human Factors and Ergonomics (HFE) Area, 2011). Here only longitudinal acceleration due to the brakes (m/s^2) is measured.
	Mean Driver Vehicle Speedometer Value	Mean Driver Vehicle Speedometer Value (kilometres/hour).

Construct	Outcome measure	Definition
	Mean Steering Wheel Angular Rate	Mean steering wheel angular rate (radians/second or degrees/second). The steering wheel rate or velocity (degrees/second) or steering wheel angular rate is speed of turning the steering wheel while doing steering movements. This variable accounts both positive and negative steering rates and these could average out to 0 indicating no steering activity (NCSU Human Factors and Ergonomics (HFE) Area, 2011).
	Minimum Time to Collision Vehicle	Minimum time to collision (seconds) between the driver's vehicle and all vehicles in the driver's direction.
	Minimum Range Vehicle	Minimum range (metres) between the driver's vehicle and all vehicles in the driver's direction
	Absolute Value of the Lateral Lane Position	The absolute value of lateral lane position of the vehicle with respect to the roadway dividing line. This only shows the magnitude of lateral lane position and not the specific direction.
	Minimum Time to Collision Cross Traffic	Minimum time to collision (seconds) between the driver's vehicle and all cross traffic vehicles in the driver's direction.

Construct	Outcome measure	Definition
	Minimum Range Cross Traffic	Minimum range (meters) between the driver's vehicle and all cross traffic vehicles in the driver's direction
	Minimum Time to Collision Pedestrian	Minimum time to collision (seconds) between the driver's vehicle and all pedestrians that are within the extents of the driver's vehicle
	Minimum Range Pedestrian	Minimum range (meters) between the driver's vehicle and all pedestrians that are within the extents of the driver's vehicle
	Absolute Value of Lateral Acceleration	Absolute value of lateral acceleration represents the magnitude of the abrupt lateral acceleration (m/s2) regardless of the direction (left and right) of lateral acceleration.
	Absolute Value of Steering Wheel Angle	Absolute value of steering wheel angle (degrees). This is the absolute value of Steering wheel angle input (degrees) and only shows the magnitude of the driver's steering wheel input and not the specific direction.
	SD Lateral Lane Position	SD of Lateral Lane Position of the driven vehicle with respect to the roadway dividing line

Construct	Outcome measure	Definition
	Mean Steering Wheel Angle Input	Mean Steering wheel angle input (degrees). This variable includes the direction of steering wheel input as well
	SD Steering Wheel Angle Input	Standard deviation (SD) of Steering wheel angle input
	SD Driver Vehicle Speedometer Value	Standard deviation (SD) of Vehicle Speedometer Value
	Total number of off road crashes	The off road crash is counted when the driver steers the vehicle too far off the road and only counts the occurrences of crashes off the roadway (NCSU Human Factors and Ergonomics (HFE) Area, 2011). Here the events when centre point of the car exceeded the off road buffer distance of 1 metre were also counted as an off-road crash.
	Total number of collisions	Total number of contacts with another vehicle, a barrel, a barrier or a collision block
	Total number of pedestrians hit	The number of collisions with pedestrians

Construct	Outcome measure	Definition
	Total number of speed exceedances	Total number of instances that the vehicle exceeded the maximum posted speed limits of 120, 80, or 50 km/h
	Total number of centreline crossings	Total number of instances that the any portion of the driver's vehicle crossed the roadway centreline.
	Total number of road edge excursions	Number of instances where any portion of the drivers' vehicle crossed the roadway and entered the shoulder

Table 5.4 Primary outcomes of interest

Construct	Name of measure	Specific index
Objective Sleepiness	EEG-related outcome measures	Mean alpha (α; 8–13 Hz) power (mV^2)
		SD of alpha (α; 8–13 Hz) power (mV^2)
		Mean theta (θ; 4– 8 Hz) power (mV^2)
		SD of theta (θ; 4– 8 Hz) power (mV^2)
	ECG-related outcome measures	Mean beat-to-beat interval (millisecond)
		SD of beat-to-beat interval (millisecond)
		Mean heart rate (beat/minute)
		Proportion of high-frequency heart rate variability (HF 0.15 to 0.40 Hz) to Low-frequency heart rate variability (LF 0.04 to 0.15 Hz), HF/LF
	PEBL Psychomotor Vigilance Task (PPVT) performance	Percentage of lapses (%)
		Percentage of correct responses (%)
		Mean of the slowest 10% of reciprocals of reaction time (s^{-1})
		Mean reciprocals of correct responses and lapses (s^{-1})

Construct	Name of measure	Specific index
Subjective Sleepiness	Subjective Sleepiness outcome	Karolinska Sleepiness Scale (KSS)
Driving performance	Driving performance outcome measures	Absolute value of lateral acceleration (meters/second^2)
		Absolute value of steering wheel angle (degree)
		SD of lateral lane position (metre)
		Total number of collisions,
		Total number of road edge excursions,
		Total number of off-road crashes,
		Total number of speed exceedances

SD=Standard deviation

Objective outcome measures

Objective sleepiness was measured in three domains: EEG and ECG-related outcomes as well as PPVT-related outcome measures.

EEG outcome measures were theta (θ; 4–8 Hz) and alpha (α; 8–13 Hz) absolute power (mean and SD). Absolute power refers to the total energy intensity of an electrode on a certain brain region at a certain frequency band (Machado et al., 2007). These two frequency bands were chosen because they have shown sensitivity to sleep loss in experimental studies, so that an increased activity in EEG alpha (Eoh et al., 2005; Gillberg et al., 2003; Lowden et al., 2009), or both alpha and theta bands (Åkerstedt & Gillberg, 1990; Horne, J.A & Reyner, 1996; Kecklund & Åkerstedt, 1993; Otmani et al., 2005; Torsvall & ÅKerstedt, 1987) have been adopted as indices of sleepiness. Accordingly, in *light* and *caffeine* studies these two frequency bands have been adopted as indices of alerting effects of light/caffeine with a decrease in alpha and theta power (Cajochen, Christian et al., 2000; Figueiro, M.G et al., 2009).

ECG-related outcome measures included beat-to-beat interval (mean RR), heart rate and the HF/LF ratio (the proportion of high-frequency heart rate variability to low-frequency heart rate variability). Beat to beat interval is defined as variations between consecutive heartbeats (Tarvainen et al., 2014). A review study highlighted that increase in mean RR is related to driver sleepiness (Borghini et al., 2014).

Heart rate (beat/minute) has shown a decrease during sleepy night time driving (Lal & Craig, 2001$_{(a);}$ Riemersma et al., 1977) or daytime drives (Borghini et al., 2014; Liang et al., 2007). LF/HF ratio calculated from RR tacho-grams refers to the proportion of high-frequency heart rate variability (0.15 to 0.40 Hz) to low-frequency heart rate (0.04 to 0.15 Hz). LF/HF heart rate variability has been found to decrease with increasing sleepiness (Baharav et al., 1995; Tarvainen et al., 2014). This attenuation has also been confirmed by some driving experiments (Liang et al., 2007; Michail et al., 2008).

Driver PPVT performances were measured with 4 indices including percentage of lapses, percentage of correct responses, mean reciprocals of reaction times, and mean of the reciprocal of the slowest 10% 1/RT.

Percentage of lapses is traditionally indicative of reduced behavioural alertness (Loh et al., 2004; Sforza et al., 2004) and is defined as the ratio of responses to the stimulus with reaction times slower than 500 milliseconds to the total number of responses, multiplied by 100. Correct responses refer to reaction times between 100 and 500 milliseconds. Percentage of correct responses represents the ratio of correct responses to the total number of responses multiplied by 100.

Mean reciprocals of reaction times is traditionally known as the reaction speed (Lamond et al., 2008). Based on reciprocals of reaction times two more indices were selected: mean of the reciprocal of the slowest 10% 1/RT and mean of reciprocals of lapses and correct responses. Mean of the slowest 10% of reciprocals of reaction times (1/s) was calculated from correct responses as mean of reciprocally transformed top 10% of the slowest responses multiplied by 1000 (Sforza et al., 2004). Higher values of mean of the slowest 10% of reciprocals of reaction times demonstrate better performance (Loh et al., 2004; Sforza et al., 2004).

The above mentioned outcome measures are sensitive indices of PPVT to sleep loss. Severe sleep loss has been found to increase the number of lapses and mean reciprocals of reaction time (Lamond et al., 2008). Additionally, the relationship between number of lapses and higher crash risk rates has been repeatedly demonstrated (Arnedt et al., 2005). For instance, attention lapses from sleep loss have been correlated with both lane drifting (Jackson et al., 2013; Philip et al., $2005_{(a)}$) and road crashes on the simulator (Dinges et al., 1997; Ting et al., 2008).

Subjective outcome measure

Subjective alertness was assessed using the Karolinska Sleepiness Scale (KSS), a nine-point sleepiness rating scale. This scale is one of the most commonly used sleepiness scales (Shahid, Shen, & Shapiro, 2010) measuring situational sleepiness. The KSS has been shown to be sensitive to changes of sleepiness in response to environmental factors, sleep loss, time of day (including circadian effects), and the effects of drugs (Shahid et al., 2010). The scale consists of 9 numeric ratings corresponding to a unique verbal description for the particular state of sleepiness (Åkerstedt & Gillberg, 1990) including:1 = ‘extremely alert’, 2 = ‘very alert’, 3 = ‘alert’, 4 = ‘rather alert’, 5 = ‘neither alert nor sleepy’, 6 = ‘some signs of sleepiness’,

7 = ‘sleepy, no effort to stay awake’, 8 = ‘sleepy, some effort to stay awake’, 9 = ‘very sleepy, great effort to keep awake’ (Reyner, L. & Horne, 2002). Because of its nature as a measure of instantaneous sleepiness it is difficult to estimate the test-retest reliability for the KSS due to difficulties in maintaining identical situations in both test and retest sessions. Nevertheless, the KSS has shown a high reliability in sleep deprived subjects, such that there was no significant difference between two nights of sleep loss with one week wash out between them (Gillberg, Kecklund, & Åkerstedt, 1994). Furthermore, the KSS has demonstrated high validity against performance data during these two nights of sleep loss (Gillberg et al., 1994). The KSS has also been validated against EEG correlates of sleep and other behavioural variables (Åkerstedt, Kecklund, & Knutsson, 1991; Kaida et al., $2006_{(a)}$).

Driving performance outcome measures

The primary-interest driving performance outcome measures included absolute value of lateral acceleration, absolute value of steering wheel angle, the standard deviation of lateral lane position, total number of collisions, total number of road edge excursions, total number of off-road crashes and total number of speed exceedances.

The absolute value of lateral acceleration is the average magnitude of abrupt lateral acceleration (m/s^2) regardless of the direction (left and right) of lateral acceleration.

Lateral lane position was defined as the distance of centre point of car from the road dividing line. An off-road crash was counted when the centre point of the car crossed the road edge by 1 metre. Additionally, all instances that any portion of the car crossed the road edge were accounted for as road edge excursion. The number of collisions were counted when the driver hit another vehicle including cross traffic vehicles, pedestrians, vehicles in either lane of traffic, any collisions with collision blocks and vehicles in the rear view mirror (NCSU Human Factors and Ergonomics (HFE) Area, 2011).

The absolute value of steering wheel angle in degrees indicates the magnitude of the steering wheel’s input (degrees). This measure does not include the direction of steering wheel input. Steering wheel movements increase in amplitude when sleepy (Brown, I. D., 1997; Lal & Craig, $2001_{(a)}$), particularly absolute steering wheel inputs

larger than 10^{o} (Atchley & Chan, 2011). Steering behaviour in one study was a major indicator of driver performance when sleepy (Forsman et al., 2013). Road edge excursion (lane drifting; any part of the car out of road edge) is also very sensitive to sleep loss (Filtness et al., 2012). Off-road crash (all four wheels off the road) increases with both sleep loss and time-on-task (Filtness et al., 2012). The total number of speed exceedance events is a metric that indicates all instances of exceeding the set speed limits of 120 km/h, 80 km/h or 50 km/h within the simulator scenarios (these limits were provided to the participants via roadside speed advisory signs within the scenarios).

5.4 INTERVENTIONS

Inducing the chronic sleep loss

Two weeks prior to the experiment some small watches were attached to the participants' wrist (Philips Respironics Actiwatch®- 2, Figure 5.10). This is a 43 mm x 23 mm x 10 mm waterproof watch (to 1 m depth for 30 minutes). This device includes an accelerometer to record movements (sampling rate 32 Hz) and a light sensor and event marker to record the lights out times (Philips Respironics).

Figure 5.10. Philips Respironics Actiwatch®- 2, (adopted from Philips Respironics).

Stimulation by Light

Active Light (blue-green light) and Placebo Light (red light) were provided and delivered by Re-timer glasses (SMR Technologies, Model No. 1495000), a

commercially available product that has been independently tested for eye safety (CEI IEC62471). Re-Timer glasses are lens-free spectacle frames in one size of 200 x 140 x 55 mm. These glasses comprise two LEDs per eye (0.1 watts, with a diffuser cover) mounted on the lower rim of the frame for each eye, approximately in the middle of the visual field of each eye at a distance of approximately 12 mm from the corneal surface. Since point light sources at this very close distance are not recommended, each LED distributes an unfocused disk of light to the centre of pupil, subtending 20º angle of vision. Therefore, the two LEDs per eye lit two 20º diameter disks of light below the central or macular area when subjects view the simulator monitor (Wright, H. R., Lack, & Kennaway, 2004). These glasses have an on-board battery (i.e. wireless), with a USB port for recharging. These glasses are shown in Figure 5.11.

Figure 5.11. Re-Timer light glasses with USB port for recharging, adopted from the official Re-Timer sleep glasses website.

The illuminance can be set at a high level 506 Lux (lm/m²) with intensity 230 µW/cm² or at a low level 315 Lux (lm/m²) illuminance and 143 µW/cm² intensity. In this experimental study the high level of blue-green light was administered. Using a reflected light method the spectral output of the high level of blue-green light was measured in photometric and daylight laboratory of Queensland University of Technology. As it is seen in Figure 5.12 the dominant wavelength of the blue-green light is at about 520 nm.

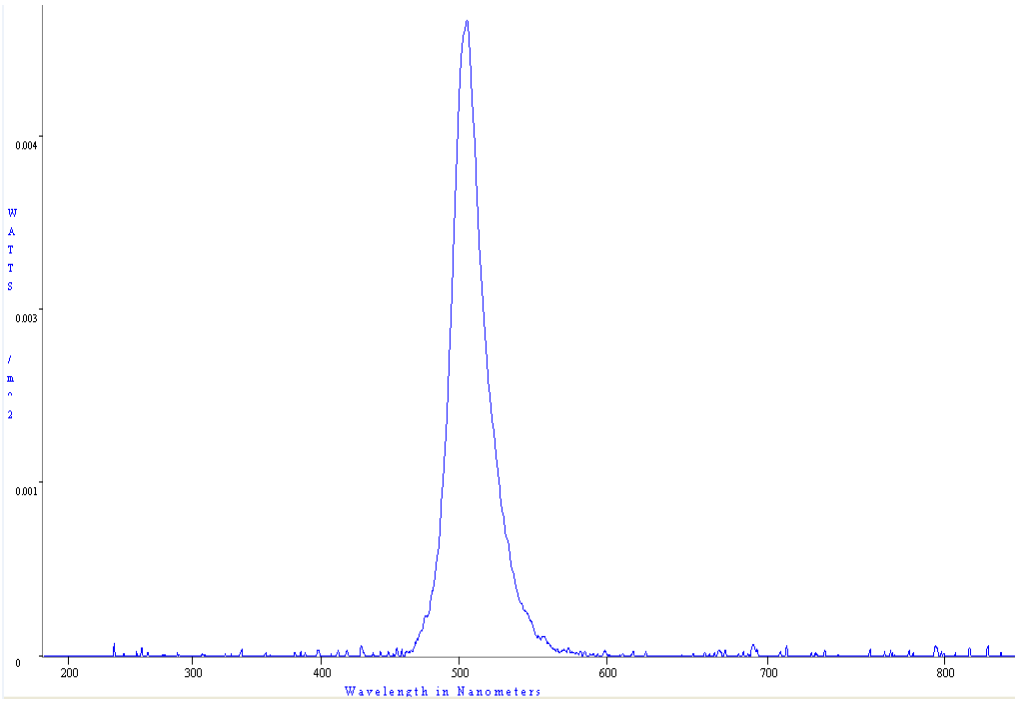

Figure 5.12. Spectral distribution of blue-green light emitted by the Re-Timer glasses, the horizontal and vertical axes show the wavelength in nanometre and power in W/m^2 respectively.

Some studies have reported a dose-response relationship between light intensity and alerting effects such that shorter wavelengths and higher intensities of light have more alerting effects than those of long wavelengths or low intensities (Cajochen, Christian et al., 2000). However, understanding of the relationships between light wavelength, intensity and duration that might have optimal alerting effect is still emerging, with new evidence that different profiles may have differential effects. The objective of this research was to examine the alerting effect provided by off-the-shelf, safe, and commercially available light technologies such as Re-Timers. These devices were designed, with empirical support, to provide an optimal compromise between effective phase shifting and visual comfort, and their form factor provided an opportunity to assess their impact on alertness *while driving*.

5.4.1 **Stimulation by Caffeine**

In the Active Caffeine condition, a dose of 100 mg caffeine was administered via 'Stay Alert' caffeinated chewing gum originally developed by the Walter Reed Institute of Army Research (source: MMI Outdoor, Montgomery, AL, USA) (Figure

5.13). These gum pieces are available in 100 mg and 200 mg doses per piece, flavoured by arctic mint, mint, or cinnamon. The higher dose of this gum (200 mg) has been shown to increase the alertness among sleep-deprived participants (Killgore, Kamimori, & Balkin, 2011). In the current study 100-mg dose gums were administered. While 100 mg is not regarded as a high dose of caffeine (Denaro et al., 1990), the American Academy of Paediatrics recommends that adolescents get no more than 100 mg of caffeine a day. This dose is equivalent to a regular 'flat white' or many caffeinated 'energy drinks', and thus represents typical caffeine intake by drivers when they feel sleepy. The absorption profile of caffeine from this source differs from that of beverage-based dosage - within 5 min of administration approximately 85% of the caffeine within the caffeine gum was absorbed into the blood circulation system (Novum, 1997). Similarly, the Walter Reed Army Institute of Research found a faster absorption and a faster bioavailability of caffeine in chewing gum than those of capsules (Kamimori et al., 2002). Overall, chewing gum has shown rapid absorption and is the most reliable method of administering caffeine.

In this experimental study the caffeinated chewing gums were administered 15 min before driving to provide ample time to reach maximum blood concentrations (Taillard et al., 2012). The same schedule was used for decaffeinated chewing gum in the Placebo Caffeine condition. Placebo Caffeine was provided by a non-caffeinated chewing gum identical in appearance to the Active Caffeine gum and not distinguishable by taste.

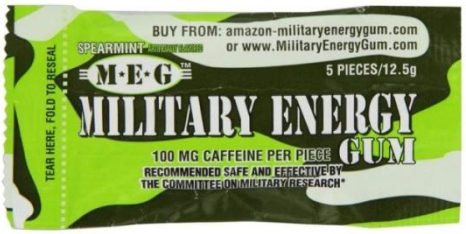

Figure 5.13. Stay Alert caffeinated chewing gums.

5.5 PROCEDURE AND TIMELINE

In this study a multi-step approach was used: including study advertisement, screening and recruitment of participants, ambulatory monitoring of sleep-wake, preparing the laboratory and administration of the tests.

Figure 5.14 shows the flowchart of the experimental study. Each step of the experimental study is explained below:

5.5.1 **Recruitment and screening**

Recruitment of participants was conducted via a three-step screening method including initial phone call screening and main screening session. These screening steps were as follows:

Phone call screening

The advertisement was undertaken by posting an approach email and flyer to University-based undergraduate student, postgraduate student, and staff email lists. The research was also advertised publically via the Centre for Accident Research and Road Safety's website and via Facebook. The approach email and recruitment flyer are shown in Appendix G and Appendix H, respectively.

After receiving expressions of interest, the Participant Information Sheet (Appendix I) was emailed to the prospective participants. Interested participants sent an email to the researcher with their availability for phone call screening. Using the Phone Call Screening Checklist (Appendix A), the researcher assessed the eligibility of participants by phone and gave them instructions for attending the main screening session at the laboratory.

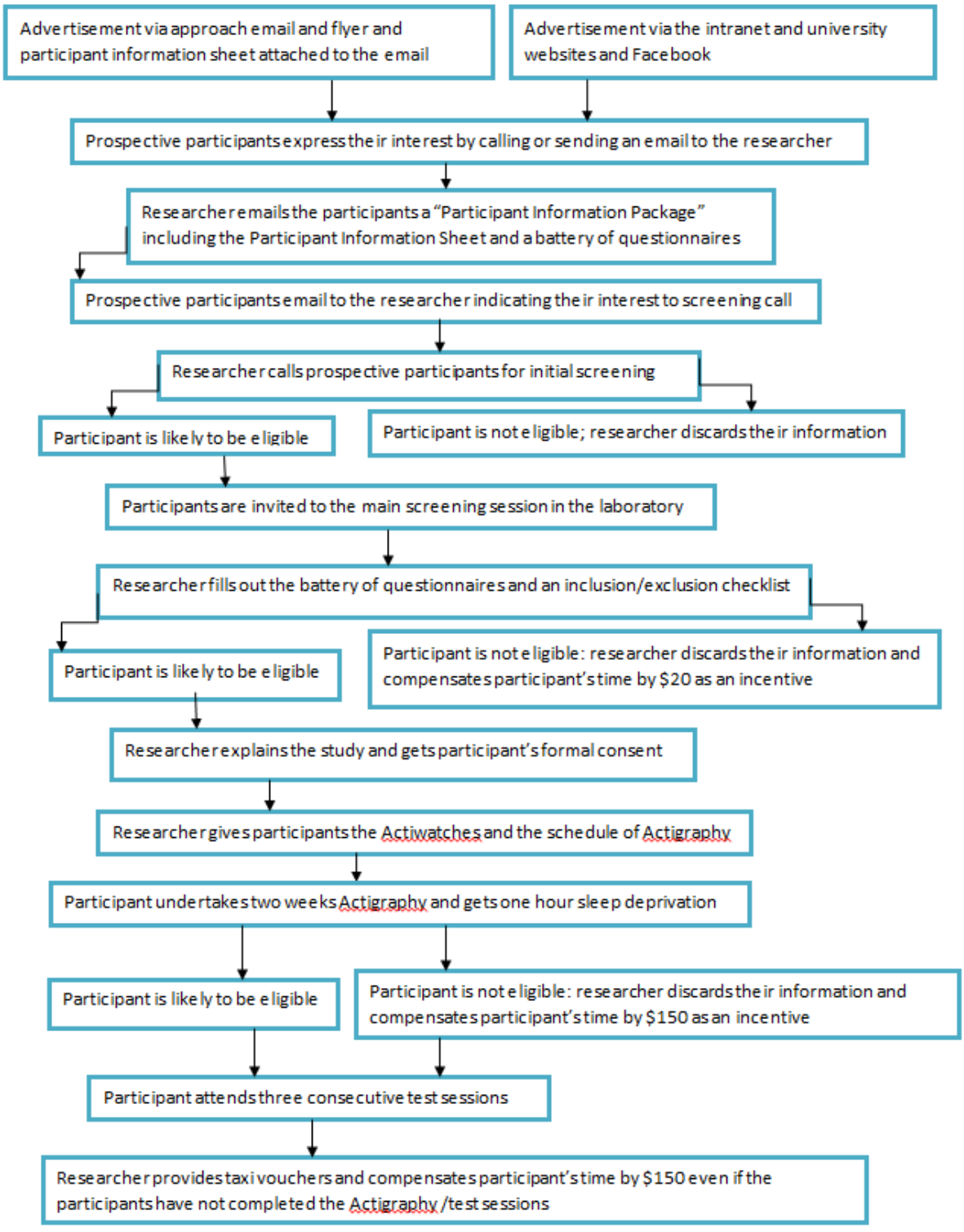

Figure 5.14. Flowchart of the procedure of the experimental study

Main screening session

Potential participants attended the laboratory, where their eligibility was assessed with the Lifestyle Appraisal Questionnaire (LAQ), Horne-Ostberg Morningness–Eveningness Questionnaire (MEQ), The Epworth Sleepiness Scale (ESS) and the screening checklist. Eligible participants were given a formal consent form to sign (Appendix J). It should be noted that the exclusion criteria did not rule out any interested participants as all respondents were mostly healthy and young adults. Participants then undertook a familiarization trial on the simulator using a training scenario for at least 5 minutes, and also completed a 5-minute trial PPVT. At the end of the screening session, participants were provided with a sleep-wake diary. The diary was specific to each person, instructing them on their Actigraphy time periods and test sessions, sleep and wake times and alcohol/caffeine intake requirements during the Actigraphy period and on the test days. A sample sleep/wake diary is presented in Appendix K. In order to run the screening session smoothly, all above-mentioned activities were followed as indicated in a Screening Checklist presented in Appendix K.

5.5.2 **Sleep deprivation protocol**

During the two weeks prior to the experiment, Actigraphic monitoring of activity and sleep-wake behaviour was conducted to monitor participant sleep-wake behaviour.

Participants were required to maintain their sleep- wake time between 11 p.m. ± 30 min and 7 a.m. ± 30 min during the first week to establish the baseline sleep-wake habits. Participants were instructed to text message the researcher immediately after waking up every day to ensure their adherence to the sleep-wake protocol. During the second week (the sleep restriction week), a progressive partial bedtime restriction regime was adopted. From day 1 to day 4 in this week, participants gradually restricted their bedtime by 15 minutes per night. They did this via an earlier wake up time hence participants' wake time was 6 a.m. by the fourth night of sleep restriction. From day 5 to day 7 the participants maintained this new sleep-wake schedule. No naps were allowed during these two weeks. Participants were supposed to consume normal caffeine (less than 2 cups of coffee per day), but no caffeine was allowed for at least the 9 hours before starting tests on the laboratory days. Figure 5.15 illustrates

bedtimes across this period. The time between 6 a.m. and 7 a.m. is shown in 15- min intervals. The black, yellow and red parts represent sleep, wake, and sleep restriction times, respectively.

In the first test day, after 11 nights of Actigraphic monitoring, Actigraphy data were downloaded and the Actigram was visually inspected to ensure the compliance of participants with the sleep-wake protocols. Participants wore the Actiwatches again for the next three days and were asked to maintain their restricted bed time (7 hours total bedtime).

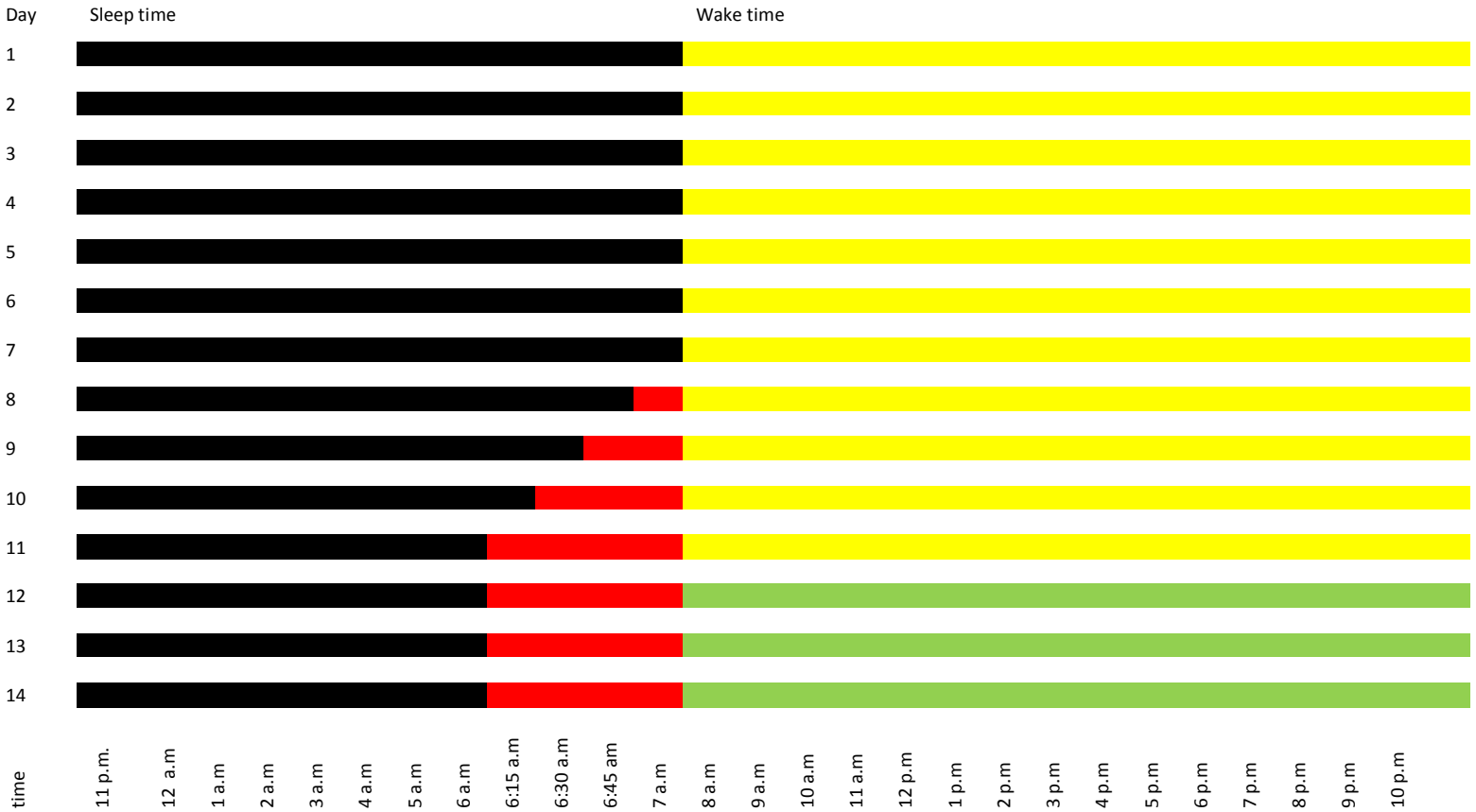

Figure 5.15. Time line of ambulatory sleep-wake during Actigraphy, Black: Time in bed, Yellow: wake time during the first 11 nights, Red: sleep restriction time, Green: wake time on three consecutive test days.

5.5.1 **Laboratory Environmental Controls**

Ambient lighting

The test sessions were conducted in a light and temperature controlled laboratory environment. Standard room lighting was provided by overhead fluorescent troffers, but ambient lighting during the study phase was provided by Philips Living Colours Generation 2 LED lamps. These lamps were used to provide dim red light background lighting inside the laboratory. This system is able to deliver light of defined spectra with control for intensity (Figure 5.16).

Figure 5.16. Philips Living Colours Generation 2 LED (adopted from Amazon.com).

A calibrated light meter (GOSSEN MAVOLUX, Model 5032B USB) was used to determine levels of ambient light inside the laboratory. This device is classified according to DIN 5032-7 and CIE 69 with initial sensitivity of 0.01 lux, allowing measures of extremely low light intensities and includes a photocell to measure general illuminance levels (Figure 5.17).

Figure 5.17. Light metre MAVOLUX (adopted from http://www.gossen-photo.de/english/licht_p_mavolux.php)

Temperature and humidity were continuously monitored with HOBO tem/RH (UX100-003) loggers, and maintained between 20-24 ^{o}C. The laboratory space was also prepared for the study by covering mirrored internal windows with black acoustic foam to prevent intrusion of any noise and light. An adjustable (for height and lay-back) and comfortable driving seat was provided to enhance participant's driving experience (KAB Controller 24-hour operator chair).

5.5.2 **Test session**

Before each test session the researcher prepared the lab using a "Test Session Checklist". This checklist comprised of three sections - *before test, during test* and *after test* to run the test smoothly and on time. A sample Test Session is presented in Appendix M.

During the last three days of the second week of sleep-wake monitoring (from day 5 to day 7) the participants underwent one test session per day as follows:

- On day 5 = Test session 1
- On day 6 = Test session 2
- On day 7 = Test session 3

Each test session lasted approximately 3 hours. The timetable of one test session is shown in Table 5.5

Table 5.5 Timetable of a test session

Time of day	Task
8:30 am	Arrival at laboratory, EEG and ECG electrodes placement
9:00 am	Adaptation to the darkness under a dim red light
9:15 am	Receiving the placebo caffeine (decaffeinated chewing gum)
9:23 am	Completion of a 5-min PPVT
9: 30 am	Reporting subjective sleepiness and driving on the simulator with red light Re-Timer
10 am	Reporting subjective sleepiness and completion of a 5-min PPVT
10:05 am	Presentation of either caffeinated or decaffeinated chewing gum
10:20 am	Simulated drive with either blue-green or red light Re-Timers
10:50am	Reporting subjective sleepiness and completion of a 5-min PPVT
10:55 am	End of the study

On the day of each test session participants woke up at 6 a.m. and arrived at the laboratory at 8:30 a.m. Instrumentation of participants (placement of EEG and ECG electrodes) was undertaken immediately upon arrival. EEG and ECG were then continuously recorded from 9 a.m. throughout the experiment. Drivers were seated on an ergonomic and adjustable seat to reduce their movement from any discomfort while driving. The EEG and ECG electrodes were connected to the data recorder attached to the back of the head rest on the seat, and drivers were instructed not to make unnecessary movements.

At 9 a.m. the overhead light system in the laboratory was switched off and the indoor lab area was maintained under a dim red light (< 2 lux) for the entire test period. Participants were seated under this dim light for a 30 min rest/adaptation period. There were two reasons for this adaptation period:

1. Since the blue-green light provided by the Re-Timer device was relatively low intensity (in the context of intensity variation between outdoor sunlight and indoor light), typical background light may swamp the alerting effects of light; therefore, the presentation of blue-green light was preceded by an adaptation period to near-darkness (< 2 lux dim red light) to provide blue-green light with the opportunity to exert its effects. This approach was adopted by Chang et al. (2013) to compare the alerting effects of light after different light exposure histories. They found more sustained alerting response to light when preceded by 1 lux exposure compared to 90 lux light exposure.
2. The 30-min near-darkness period was intended to allow time for the autonomic arousal system to adapt to darkness and to the seated position. A dim red light was adopted because absolute darkness (without any visible light) might act as stressor for some participants.

Participants were given Placebo Caffeine (decaffeinated chewing gum) at 9:15 a.m., 15 minutes before their first drive. The reason for this 15 min interval was to treat the administration of Placebo Caffeine in exactly the same way as Active Caffeine. Participants were blind to the order of administration of caffeine, and were not informed that the first administration was always the placebo.

At 9:23 a.m. participants completed a 5-min version of the PPVT before reporting their subjective sleepiness on the Karolinska Sleepiness Scale. At 9:30 a.m. the EEG and ECG electrodes were doubled checked and participants were asked to put on the red-light Re-Timer glasses and to start driving. Participants began the first 30-minute simulated drive under Condition 4 (Placebo Caffeine and Placebo Light).

At 10:00 a.m. participants reported their subjective sleepiness immediately after the drive and undertook the PPVT. At 10:05 a.m. subjects were given either caffeinated gum or decaffeinated gum (depending on the counterbalanced condition assigned to that test session) and were asked to rest for 15 minutes.

At 10:20 a.m. participants were asked to put on either blue-green or red light Re-Timer glasses (depending on the counterbalanced condition assigned to that test session) and were asked to drive for 30 minutes on the same driving scenario as their first drive.

At 10:50 a.m. participants reported their subjective sleepiness immediately after completing the second simulated drive and undertook a 5-min version of the PPVT. At 10:55 a.m. the researcher stopped the recording of the EEG and ECG and all electrodes were detached. Participants were reminded of all necessary instructions. The test session protocols were repeated for the next two days. The light exposure was provided only during two 30- minute drives. The PVT testing was conducted under ambient room light (red < 2 lux) shortly after cessation of the experimental light exposure in each condition. Figure 5.18 exhibits the laboratory setting and a participant before switching off the overhead light system.

Figure 5.18. The laboratory setting and a participant before switching the light system off (permission granted from the participant)

5.6 DATA TREATMENT

5.6.1 **EEG data**

EEG data was recorded by the Compumedics Somté data recorder at 256 Hz. This device contains a Compact Flash Card where the recorded data is saved. Using Data Card Manager 3 software, EEG data were converted to Compumedics Profusion (Version 3) format for export in 30-second epochs. The EEG channels (central and occipital) were filtered with a high pass 0.3 Hz and low pass 30 Hz filters. Next, the EEG data were processed with Profusion 4 software. This software is used for reviewing, editing and reporting EEG data. The EEG data underwent Power Spectral Analysis (PSA) using this software. In this method, the EEG signal in each channel is processed using a Fast Fourier Transform to identify signal amplitude for each specified frequency band during each 30-s epoch, and to quantify the overall power spectra trends in the EEG data (Ktonas & Gosalia, 1981). The EEG and ECG data were also visually inspected to edit out any artefacts from head movements and blinking. The output containing all EEG data for the entire test session was saved in ASCII (text file) format and was imported to an Excel file for further manipulation.

After identification of data in the Excel file corresponding to the first and the second drive periods, MATLABR2014b software (The MathWorks) was used to calculate four parameters of minimum, maximum, mean and the standard deviation of these data for each session. This process of identifying the synchronised rows of EEG data with two simulated drive times was undertaken to attribute alpha and theta EEG power indices to the corresponding driving conditions. The output of MATLAB was saved in another Excel sheet. These data were re-sorted by condition type before being copied into an SPSS file for statistical analysis.

5.6.2 **ECG data**

ECG data were recorded along with EEG by Compumedics Somté data at 256 Hz and were converted to Profusion format in 30-second epochs using Data Card Manager 3 software. The Profusion (version 4) software was used to filter ECG data at the high pass 0.3 Hz and low pass 30 Hz, and to save ECG raw data to European Data file (EDF) format. Further analysis was conducted with Kubios HRV (version 2.2) software developed by the Biosignal Analysis and Medical Imaging Group in the University of Eastern Finland (Biosignal analysis and medical imaging group, 2014). Kubios HRV is specific software for studying and reporting heart rate variability (HRV). The software calculates values of time-domain or frequency-domain variables of HRV. When opening an ECG EDF file with this software, the heart beat-to-beat intervals (RR) are identified in one-minute intervals as a default. These data were treated in a similar fashion to that used for EEG data, such that time intervals corresponding to the two driving sessions were identified.

Accuracy of R-wave peak detection was assessed by visual inspection of the files, and were mostly correctly identified and marked in these young and healthy participants. A ‘low’ level of filtering only was applied to all ECG/HRV files to remove artefacts in the data. The Kubios HRV output report was saved in TXT format for further review and processing in Microsoft Excel (2010). From the time-domain variables, mean and standard deviation of the beat-to-beat intervals and heart rate were reported. From the frequency domain outputs, low frequency heat rate variability (LF, 0.04-0.15), high frequency heat rate variability (HF, 0.15-0.4), and

LF/HF data were reported. These data were sorted by condition type and copied into SPSS file for statistical analysis. Figure 5.19 represents an EDF file opened by Kubios software and two time intervals for sampling of variables.

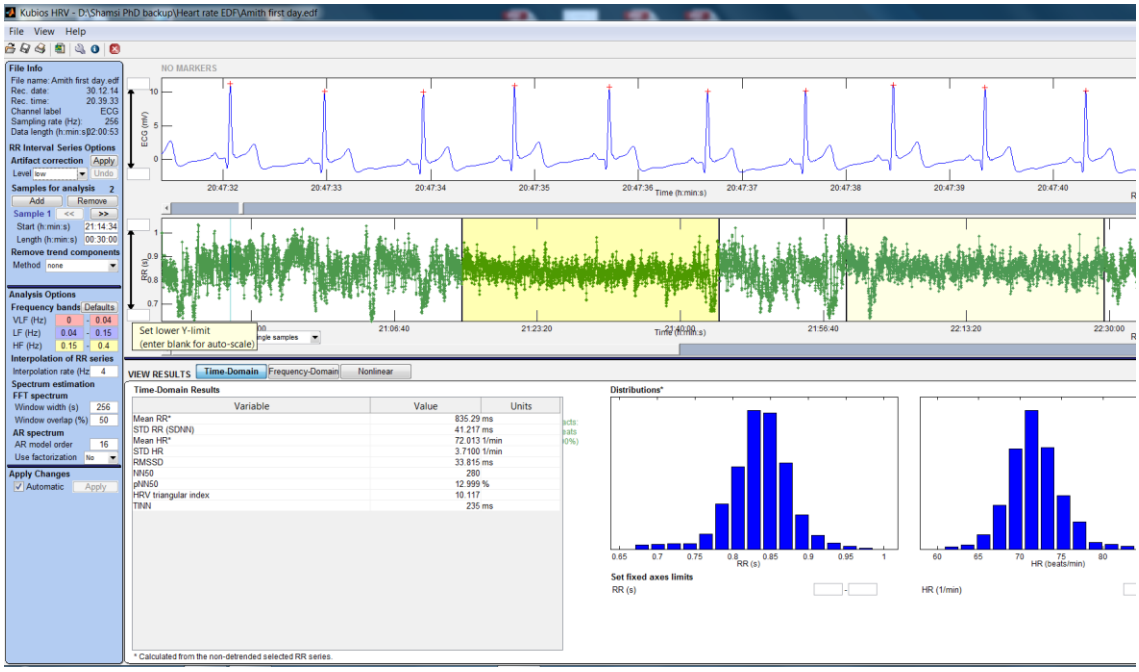

Figure 5.19. An ECG data file opened in the Kubios HRV software. The plot in green shows beat-to-beat intervals for the entire recording period. The section marked in yellow represents the sampling intervals (two driving sessions). The plot in blue (upper panel) shows the full ECG waveform sampled for R wave peak detection (peak detection marked as a red cross).

5.6.3 **PEBL Psychomotor Vigilance Task (PPVT) data**

PPVT data was recorded in TXT file format for every 5-min PPVT session. Therefore, in each test session for each participant there were three PPVT text files. These files were imported into a XLSX file and data were sorted from the fastest to slowest reaction times (RTs).

Reaction times were transformed to reciprocals of RTs in accordance with standard methodology (Dinges & Kribbs, 1991). The rationale for using reciprocals of reaction times was that they provide normal distribution of data and highlight slowing in the optimum and intermediate responses and substantially hinder the contribution of long lapses (Basner & Dinges, 2011). Since in the PPVT the stimuli

appear at variable intervals between 2-12 seconds, there was a different number of RT trials completed across each 5-minute PPVT task. Therefore, the *percentage* of correct, false and lapse responses were calculated to standardised these responses. All calculated data were copied into a SPSS file for statistical analysis.

5.6.4 **Driving performance (STISIM Drive) data**

Driving performance outcome measures (25 variables) were extracted as raw data in a TXT file for each driving session. This report started with all commands performed during the scenario, and all blocks of data saved and ended with values of different variables, sorted in the order that had been predefined. Using MATLABR (2014b) a specific code was developed to calculate the mean, standard deviation, minimum and maximum of values of each variable for all rows of data and these secondary data were saved in another Excel sheet. Using this method, data for each participant were saved in a XLSX file containing six Excel sheets for a total of six driving sessions. In the next step data were sorted from condition 1 to condition 3 in another Excel sheet. It should be noted that the last six variables described discrete events; the total number of off road accidents, total number of collisions, total number of pedestrians hit, total number of speed exceedances, total number of centreline crossings and total number of road edge excursions. These data were entered to a XLSX file separately before copying all the data to SPSS file for statistical analysis.

5.6.5 **Subjective sleepiness data**

Subjective sleepiness scores were recorded three times during each test session and the KSS responses were extracted and entered to a XLSX file before being copied into an SPSS file.

5.6.6 **Demographic and Actigraphic data**

Demographic data including participant code, age, gender from questionnaires, as well as Actigraphic data such as time in bed (hours), total sleep time (hours) and

sleep efficiency from Actiware software were entered to SPSS for descriptive statistical analysis.

5.7 ANALYSIS

Statistical analysis of data was performed using Statistical Package for Social Sciences software (IBM SPSS version 22, (IBM)). Demographic, Actigraphic, KSS, and PPVT variables were entered into one SPSS file due to the correspondence between the recording times of the two latter variables. Other variables such as EEG, ECG and the driving performance data were entered in a separate SPSS file. The data sets were labelled with a consistent participant identifier and with other data codes defined in the data dictionary. The method for data setup in SPSS for demographic, Actigraphic, KSS and PPVT variables is presented in Appendix N and for the EEG, ECG, and driving performance outcome measures in Appendix N.

5.7.1 **Missing data**

There were no missing values for KSS and PPVT data. The EEG recorded on the first test day was missing for two participants (code 301 and 311) due to technical problems with the data flash card. ECG data were missing for the first day (code 301 and 311) and the second day (code 301, and 303) due to technical problems with the data flash card and due to a detached ECG electrode caused by excessive movement of the participants. Some ECG data (code 301, 313 and 317) were extreme data that were identified as missing data in the SPSS data file. Driving performance data were missing only for one participant (code 324) for two drives on the second day due to running the scenario with the wrong configuration file. Actigraphy data were missing for two participants (code 308 and 329) due to faulty Actiwatches. All missing data were valued as N/A in the XLSX files. Missing data in SPSS files were defined later with discrete values. All non-time missing data were defined as 999999.00000. For timed missing data such as time in bed or sleep time the missing data were defined with two discrete values of either 0:00:00 or 9:59:59.

5.7.2 **Data analysis**

All outcome measures in this study were treated with a 2 x 3 repeated-measures, within-subjects Analysis of Variance (ANOVA). The first factor was "Placebo vs Intervention" with two levels of "Placebo (condition 4)" and "Intervention (Condition 1, Condition 2 or Condition 3, regardless of the type of condition)". The second factor was "Intervention type" with three levels including "light and caffeine in combination" (Condition 1), "light alone" (Condition 2) and "caffeine alone" (Condition 3). The Primary purpose of this analysis was to determine whether mean values of data (across all participants) after the intervention (receiving either active conditions of 1, 2 or 3 after the second drive) were different from receiving only the Placebo condition (after the first drive) and in such cases, whether or not the mean of these data was different across these three types of intervention (3 condition types). Using Mauchly's test of sphericity the equality of variances of differences between variables for two main effects of "Intervention type" and "Placebo vs Intervention" and for their interaction "Intervention type * Placebo vs Intervention" was examined. The dependent variables were the outcome measures listed in Table 5.3. The p values less than 0.05 in Mauchly's test were considered as violation of sphericity (significant differences between variances of difference between conditions). The violation from sphericity might lead to a lost power (an increased probability of a Type II error) and an incomparability of F-ratios with the tabulated values of F-ratio in SPSS outputs (Field, 2012). In case of violation of sphericity, the Greenhouse-Geisser estimate of sphericity (ε) was considered. In case of $\varepsilon > 0.75$ the Huynh-Feldt correction was taken into account (Field, 2012).

In the next step, the within-subject main effects were examined. For all non-homogenised main effects and interactions (based on the results of Mauchly's test of sphericity), the corrected F-ratios (Greenhouse-Geisser or Huynh-Feldt corrections) were considered. Finally, in case of any main effect of "Placebo vs Intervention" (significant difference between the placebo condition and interventions) a paired T-test was conducted to track the difference between each of the three types of intervention and the Placebo condition. In case of any main effect of "Intervention type" a Post-hoc T-test was conducted to track any significant differences across the

three types of intervention. A detailed explanation of ANOVA has been provided in Section 1.1.1.

5.8 ETHICAL AND TECHNICAL CONSIDERATIONS

5.8.1 **Ethical considerations**

Ethical clearance of this study was provided by the Queensland University of Technology (QUT) Human Research Ethics Committee (HREC; approval number 1300000846). Participants provided written consent to participate in the experimental study and were assured that their participation in the project was entirely voluntary and if they agreed to participate, they could withdraw from participation at any time during the project without any comment or penalty. Participants were also provided with the contact details of the QUT Research Ethics Unit to reflect any concerns or complaints about the ethical conduct of this project. Taxi vouchers for travelling to and from the test sessions were provided for participants with excessive sleepiness as a mitigation strategy. As participants were required to spend four sessions in the laboratory (one screening session and three test sessions), and to wear the Actiwatches for two weeks, their time was compensated by $150 AUD at the end of the study.

All comments and responses were treated confidentially. Any data collected as part of this project were stored securely as per QUT's Management of Research Data policy. Participants were also informed that their names would not be identified in any publications resulting from this study and agreed that non-identifiable data collected in this project could be used as comparative data in future projects or stored on an open access database for secondary analysis. They were also welcomed to request more information on the results of this study from the research team.

An annual progress report about ethical clearance awarded for the data collection of this study was submitted to QUT Human Research Ethics Committee.

There were some minor potential risks associated with participation in this study. These risks were explained in the Participant Information Sheet as follows:

a. Although polysomnography (EEG, ECG) instrumentation followed the same procedure as used in routine clinical polysomnography (i.e. sleep studies), there was a potential for minor discomfort from electrode placement.

b. Participants were likely to experience some sleepiness symptoms such as poor concentration, sleepiness during the test sessions, and potential increased sleep duration for 2-3 days after the test sessions. While the degree of sleepiness induced by the sleep time manipulation was likely to be mild, it could have some impact on the participants' activities while working or studying. Therefore, they were advised not to engage in safety-sensitive tasks such as driving if they felt excessively sleepy.

Chapter 6: The Results of the Experimental Study

The results in this chapter are presented in accordance with the research hypotheses outlined in Section 1.3. A descriptive analysis of the participant characteristics is presented in Section 6.1. Findings of the primary analyses for the alerting effects of light alone, caffeine alone, and light and caffeine in combination are then presented in Section 6.2.

6.1 DESCRIPTIVE ANALYSIS OF PARTICIPANTS

6.1.1 **Demographic characteristics of participants**

Of the 30 participants, 20 were female and 10 were male. All participants were between 18-25 years old. Participants scored an average of 6.4 on the Epworth Sleepiness Scale (all scored less than the eligibility cut-off of 10) and an average of 8.3 on the Lifestyle Appraisal questionnaire with an eligibility cut-off of 20. Participants reported overall good sleep quality, with mean score of 3.6 (less than the eligibility cut-off of 5), and sleep efficiency of 90%, on the Pittsburgh Sleep Quality Index (PSQI). Participant chronotypes were found to be mostly "intermediate" with an average score of 41.5 on the Morningness-Eveningness Questionnaire (MEQ). None of the participants were "extremely evening type", and none were excluded on that basis. Demographic characteristics of the participants are presented in Table 6.1.

Table 6.1 Demographic characteristics of the participants

	Minimum	Maximum	Range	Mean	SD
Age	18	25	7	23.5	2.5
ESS	1	9	8	6.4	2.6
MEQ	31	56	25	41.5	6.1
LAQ	2	19	17	8.3	4.1
PSQI	1	9	8	3.6	1.8
Sleep efficiency (PSQI)	70	100	30	90.3	8.5

ESS = Epworth Sleepiness Scale, MEQ = Morningness-Eveningness Questionnaire, LAQ= Lifestyle Appraisal Questionnaire, PSQI= Pittsburgh Sleep Quality Index, SD=Standard deviation.

6.1.2 **The manipulation Check**

In order to confirm the adherence of participants to their scheduled sleep-wake times, some sleep-wake parameters determined by Actigraphy, such as bed time, sleep onset latency (time taken to fall asleep), sleep efficiency, and wake after sleep onset (cumulative time of awakening during sleep period) were examined. Descriptions of these parameters are provided in Table 6.2 for the first week, the second week, and the last 4 nights of the Actigraphy measurement period.

In order to formally examine the effectiveness of the sleep deprivation regime, mean sleep times in the first week, the second week, and the last 4 nights of Actigraphy were compared using paired T-tests in SPSS version 22.

Table 6.2 Sleep-Wake parameters for the first week, second week and the last 4 nights of the Actigraphy measurement period

	First week		Second week		Last 4 nights	
	Mean	SD	Mean	SD	Mean	SD
Time in bed	7:44:02	1:08:29	7:13:40	1:19:28	7:05:18	1:20:51
Sleep Onset Latency (min)	13.5	15.9	15.0	16.3	15.9	17.2
Sleep Efficiency (percent)	81.8	7.0	82.0	7.8	82.5	7.3
Waking after Sleep Onset (min)	54.4	20.0	53.5	23.0	54.2	21.5

SD=Standard deviation

Table 6.3 provides the mean and standard deviation (SD) of sleep times across the first week (baseline), second week (incremental bedtime restriction), and the last 4 nights (experiment period) of Actigraphy. Data from two participants were missing due to technical problems with the Actiwatches. On average, the participants slept for 6:17 (h: m) per night across the first week, but in the second week they reduced their sleep time to 5:45 (h: m). Hence, in the last 4 nights, mean sleep time per night was restricted to a mean of 5:39 (h: m).

Table 6.3 Mean and SD of nightly sleep times (hours: minutes) across the three periods of Actigraphy

Sleep time	Mean	SD
Sleep time for the first week	6:17	0:48
Sleep time for the second week	5:45	1:02
Sleep time for last 4 days	5:39	1:00

SD=Standard deviation

Table 6.4 represents the paired T-test results for the differences in mean sleep times during each period of the protocol. In the second week, participants slept an average of 32 min less than they did during the first week. This difference was significant ($p = 0.003$). In the last 4 nights participants slept an average of 40 min less than during the first week. This difference was also significant ($p = 0.001$).

To investigate the effect of chronic sleep loss, a paired T–test analysis for KSS values before first drives across three days was conducted. Sleepiness levels varied slightly between 4.6 (rather alert) to KSS score 5.1 (neither alert nor sleepy) across three test days before first drives. The paired T-test of KSS scores before first drives in Table 6.5 shows that the mean KSS scores had a significant decrease of 0.5 point from the first day to the second day ($p=0.033$). This Table shows that there was no progressive sleepiness level across the three test days.

Table 6.4 Paired T-test results for sleep times in different periods of Actigraphy

Pair	Difference in sleep time (hours: minutes)		95% Confidence Interval of the Difference		t	Degree of freedom	p (2-tailed)
	Mean	SD	Lower	Upper			
Mean sleep time for the first week vs Mean sleep time for the second week	0:32	0:51	0:12	0:52	3.29	27	0.003
Mean sleep time for the first week vs Mean sleep time for last 4 nights	0:38	0:52	0:18	0:59	3.86	27	0.001

SD = Standard deviation

Table 6.5 Paired T-test results for subjective sleepiness prior to first drives on three test days

Pair	Difference in subjective sleepiness		95% Confidence Interval of the Difference		t	Degree of freedom	p (2-tailed)
	Mean	SD	Lower	Upper			
KSS first day before first drive vs KSS second day before first drive	0.53	1.30	0.04	1.02	2.23	29	0.033
KSS third day before first drive vs KSS second day before first drive	0.16	1.14	-0.26	0.59	0.79	29	0.433
KSS first day before first drive vs KSS third day before first drive	0.36	1.54	-0.20	0.94	1.30	29	0.203

SD = Standard deviation

6.2 ANALYSIS OF DATA

Six specific but related primary hypotheses (see Table 1.3) were tested to examine the alerting effects of light, caffeine, and light and caffeine in combination.

In order to test these hypotheses, a number of specific objective, subjective, and performance outcomes associated with sleepiness were selected as the primary dependent variable (outcomes) of interest. These variables were based on the findings of the narrative literature review (Chapter 2) and the systematic review (Chapter 3). These specific outcome measures are shown in Table 6.6.

Table 6.6 Primary outcomes of interest

Construct	Name of measure	Specific index
Objective Sleepiness	EEG-related outcome measures	Mean alpha (α; 8–13 Hz) power (mV^2)
		SD of alpha (α; 8–13 Hz) power (mV^2)
		Mean theta (θ; 4– 8 Hz) power (mV^2)
		SD of theta (θ; 4– 8 Hz) power (mV^2)
	ECG-related outcome measures	Mean beat-to-beat interval (millisecond)
		SD of beat-to-beat interval (millisecond)
		Mean heart rate (beat/minute)
		Proportion of high-frequency heart rate variability (HF 0.15-0.40 Hz) to Low-frequency heart rate variability (LF 0.04-0.15 Hz), HF/LF
	PEBL Psychomotor Vigilance Task (PPVT) performance	Percentage of lapses (%)
		Percentage of correct responses (%)
		Mean of the slowest 10% of reciprocals of reaction time (s^{-1})
		Mean reciprocals of correct responses and lapses (s^{-1})

Construct	Name of measure	Specific index
Subjective Sleepiness	Subjective Sleepiness outcome	Karolinska Sleepiness Scale (KSS)
Driving performance	Driving performance outcome measures	Absolute value of lateral acceleration (m/s^2)
		Absolute value of steering wheel angle (degrees)
		SD of lateral lane position (metres)
		Total number of collisions,
		Total number of road edge excursions,
		Total number of off-road crashes,
		Total number of speed exceedances

SD = Standard deviation

6.2.1 **Analysis rationale**

Figure 6.1 depicts the 2 x 3 factorial design used to test the primary outcome measures with Analysis of Variance (ANOVA). The mean values for the outcome measures before the three interventions are shown along the bottom row and represent the Placebo condition (condition 4). Mean values for the outcome measures after the three types of interventions; light alone, caffeine alone, and light and caffeine in combination is shown along the top row.

The main effects of two factors were examined. The first factor was "Placebo vs Intervention" (denoted by the vertical arrow). This factor refers to the overall effect of the intervention, regardless of intervention type. Three hypotheses were tested by analysing this factor for each of the objective, subjective and driving performance outcome indices. When there was a main effect of "Placebo vs Intervention" (a significant overall effect of the intervention), a paired T-test was conducted to test for significant differences between each intervention type and the corresponding Placebo condition. The second factor was "Intervention type" (denoted by the horizontal arrow). Intervention type refers to one of the three counterbalanced conditions of light alone, caffeine alone or the light and caffeine in combination. When a main effect of "Intervention type" was identified, a post-hoc T-test was conducted (within the ANOVA) to test for significant differences between the three intervention types, and to directly test the fourth and fifth hypotheses (comparison of relative effectiveness of light alone, caffeine alone, or light and caffeine in combination). In order to test the sixth hypothesis, in case of any main effects of the factor "Placebo vs Intervention", a post-hoc T-test was conducted.

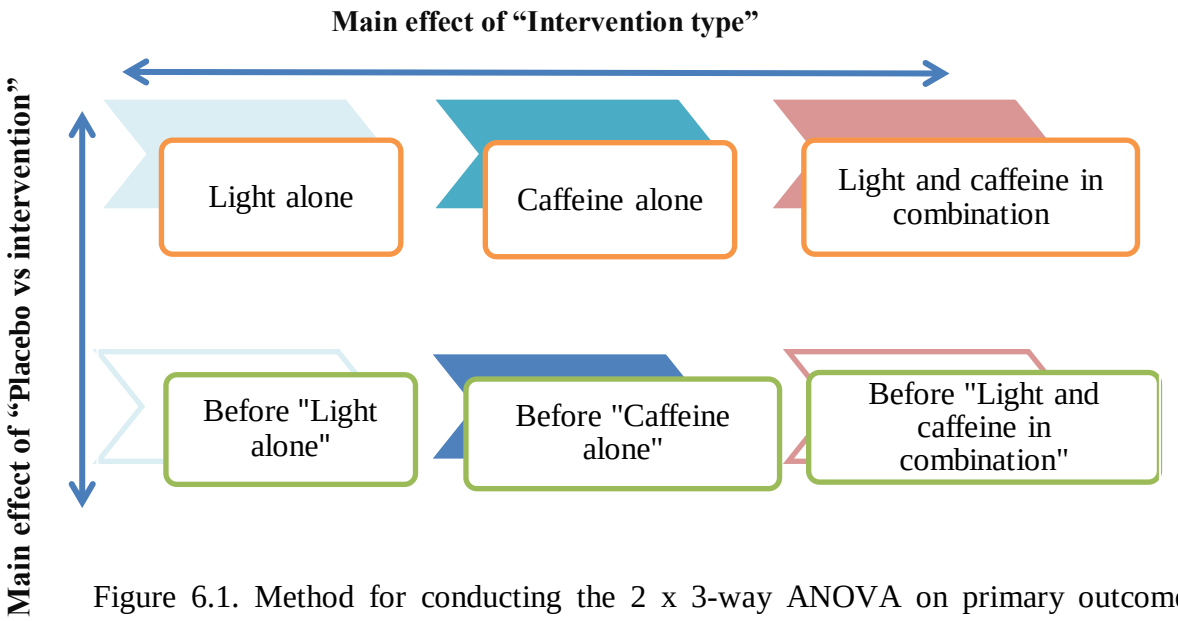

Figure 6.1. Method for conducting the 2 x 3-way ANOVA on primary outcome measures of interest.

The findings of the ANOVAs are presented in Table 6.7, Table 6.9. Table 6.7 presents the within-subjects effect, estimates of effect size and the interactions between the two factors for all primary outcome measures of interest. The results of any subsequent paired T-tests, in case of any main effect of the factor "Placebo Vs Intervention" ($p < 0.05$), are presented in Table 6.8. This table presents the comparisons of the means and standard deviations of the outcome measures in the Placebo condition (before the three types of interventions) with the corresponding values after those interventions. In this table a p-value < 0.05 indicates a significant change between the intervention and Placebo conditions.

In case of any main effect of the factor "Intervention Type", a post-hoc T-test was conducted within the ANOVA. Table 6.9 represents the pairwise comparisons between outcome measures after each type of intervention. In this table any p-values < 0.05 were associated with a significant difference between pairs of intervention types. Table 6.9 also provides the overall mean difference between the outcome measures after the Placebo condition and after the interventions.

Table 6.7 Within- subjects effects of the two ANOVA factors (Placebo vs Intervention and Type of intervention) for each of the primary outcome measures of interest

Dependent variable	Main effect/ Interaction	Degree of freedom factor	Degree of freedom Error	F-Ratio	p-value	Partial eta squared	Observed power
EEG alpha power (mV^2)	Type of intervention	2	58	1.52	0.225	0.05	0.31
	Placebo vs Intervention	1	29	2.25	0.144	0.07	0.30
	Placebo vs Intervention* Type of intervention	1.66	48.13	2.00	0.152	0.06	0.36
SD of EEG alpha power (mV^2)	Type of intervention	2	58	2.45	0.094	0.07	0.47
	Placebo vs Intervention	1	29	4.32	0.047*	0.13	0.52
	Placebo vs Intervention* Type of intervention	2	58	0.25	0.778	0.00	0.08
EEG theta power (mV^2)	Type of intervention	1.07	30.18	0.84	0.374	0.029	0.14
	Placebo vs Intervention	1	28	0.12	0.73	0.00	0.06
	Placebo vs Intervention* Type of intervention	1.27	35.69	1.12	0.311	0.03	0.19
SD of EEG Theta power	Type of intervention	2	56	0.51	0.598	0.01	0.13

Dependent variable	Main effect/ Interaction	Degree of freedom factor	Degree of freedom Error	F-Ratio	p-value	Partial eta squared	Observed power
(mV^2)	Placebo vs Intervention	1	28	1.85	0.184	0.06	0.26
	Placebo vs Intervention* Type of intervention	1.31	36.70	1.38	0.256	0.04	0.23
Mean RR (milliseconds)	Type of intervention	1.21	26.66	3.17	0.079	0.12	0.44
	Placebo vs Intervention	1	22	10.91	0.003*	0.33	0.88
	Placebo vs Intervention* Type of intervention	1.04	22.91	1.84	0.188	0.07	0.26
SD of RR (milliseconds)	Type of intervention	1.00	23.06	1.02	0.321	0.04	0.16
	Placebo vs Intervention	1	23	1.17	0.29	0.04	0.18
	Placebo vs Intervention* Type of intervention	1.00	23.02	1.09	0.307	0.04	0.17
Mean HR (beats/minute)	Type of intervention	1.66	36.56	6.02	0.008*	0.21	0.80
	Placebo vs Intervention	1	22	47.42	0.001*	0.68	1
	Placebo vs Intervention* Type of intervention	2	44	3.85	0.029*	0.14	0.66
SD of HR (beats/minute)	Type of intervention	1.14	26.34	1.52	0.231	0.06	0.23

Dependent variable	Main effect/ Interaction	Degree of freedom factor	Degree of freedom Error	F-Ratio	p-value	Partial eta squared	Observed power
	Placebo vs Intervention	1	23	0.97	0.334	0.04	0.15
	Placebo vs Intervention* Type of intervention	1.01	23.44	1.35	0.256	0.05	0.20
LF	Type of intervention	2	44	1	0.376	0.04	0.21
	Placebo vs Intervention	1	22	1	0.328	0.04	0.16
	Placebo vs Intervention* Type of intervention	2	44	1	0.376	0.04	0.21
HF	Type of intervention	1	22	0.99	0.329	0.04	0.15
	Placebo vs Intervention	1	22	1.00	0.326	0.04	0.16
	Placebo vs Intervention* Type of intervention	1	22	1.00	0.328	0.04	0.16
LF/HF	Type of intervention	1.02	22.59	0.98	0.335	0.04	0.15
	Placebo vs Intervention	1	22	0.42	0.521	0.01	0.09
	Placebo vs Intervention* Type of intervention	1.01	22.25	1.05	0.317	0.04	0.16
KSS	Type of intervention	2	58	3.51	0.036*	0.10	0.63
	Placebo vs Intervention	1	29	24.57	0.000*	0.45	0.99

Dependent variable	Main effect/ Interaction	Degree of freedom factor	Degree of freedom Error	F-Ratio	p-value	Partial eta squared	Observed power
	Placebo vs Intervention* Type of intervention	2	58	1.80	0.174	0.05	0.36
Percentage of lapses	Type of intervention	2	58	3.83	0.027*	0.11	0.67
	Placebo vs Intervention	1	29	9.52	0.004*	0.24	0.84
	Placebo vs Intervention* Type of intervention	1.35	39.18	0.01	0.946	0.00	0.05
Percentage of correct responses	Type of intervention	2	58	4.06	0.022*	0.12	0.70
	Placebo vs Intervention	1	29	9.64	0.004*	0.25	0.85
	Placebo vs Intervention* Type of intervention	1.36	39.64	0.03	0.921	0.00	0.05
Mean of the slowest 10% of 1/RT (1/S)	Type of intervention	1.75	51.00	0.07	0.904	0.00	0.06
	Placebo vs Intervention	1	29	4.81	0.036*	0.14	0.56
	Placebo vs Intervention* Type of intervention	2	58	0.13	0.871	0.00	0.07
Mean reciprocals of correct responses and lapses	Type of intervention	1.76	51.13	5.46	0.009*	0.15	0.79
	Placebo vs Intervention	1	29	2.57	0.120	0.08	0.34
	Placebo vs Intervention* Type of intervention	1.58	45.86	2.34	0.118	0.07	0.40

Dependent variable	Main effect/ Interaction	Degree of freedom factor	Degree of freedom Error	F-Ratio	p-value	Partial eta squared	Observed power
Absolute value of lateral acceleration (m/s^2)	Type of intervention	1.65	46.40	3.94	0.033*	0.12	0.62
	Placebo vs Intervention	1	28	12.29	0.002*	0.30	0.92
	Placebo vs Intervention* Type of intervention	1.63	45.87	1.00	0.36	0.03	0.19
Absolute value of steering wheel angle (degree)	Type of intervention	1.62	45.61	4.19	0.028*	0.13	0.64
	Placebo vs Intervention	1	28	16.91	0.001*	0.37	0.97
	Placebo vs Intervention* Type of intervention	1.58	44.42	1.208	0.30	0.04	0.22
SD of lateral lane position (m)	Type of intervention	1.02	29.79	0.61	0.444	0.02	0.11
	Placebo vs Intervention	1	29	0.25	0.617	0.00	0.07
	Placebo vs Intervention* Type of intervention	1.01	29.37	1.49	0.231	0.04	0.22
Total number of collisions	Type of intervention	1.58	45.82	1.10	0.326	0.03	0.21
	Placebo vs Intervention	1	29	2.08	0.160	0.06	0.28
	Placebo vs Intervention* Type of intervention	1.50	43.56	1.01	0.351	0.03	0.19
Total number of road	Type of intervention	2	58	3.72	0.030*	0.11	0.66

Dependent variable	Main effect/ Interaction	Degree of freedom factor	Degree of freedom Error	F-Ratio	p-value	Partial eta squared	Observed power
edge excursions	Placebo vs Intervention	1	29	6.96	0.013*	0.19	0.72
	Placebo vs Intervention* Type of intervention	2	58	1.25	0.294	0.04	0.26
Total number of off-road crash	Type of intervention	1.34	39.12	0.33	0.632	0.01	0.09
	Placebo vs Intervention	1	29	5.70	0.024*	0.16	0.63
	Placebo vs Intervention* Type of intervention	2	58	0.90	0.410	0.03	0.19
Total number of speed exceedances	Type of intervention	2	58	3.44	0.039*	0.10	0.62
	Placebo vs Intervention	1	29	4.50	0.042*	0.13	0.53
	Placebo vs Intervention* Type of intervention	2	58	2.15	0.126	0.06	0.42

RR = beat-to-beat interval, HR = heart rate, LF = low frequency heart rate variability, HF = high frequency heart rate variability,

SD = Standard deviation, Observed power has been computed using alpha = 0.05, * $p < 0.05$

Table 6.8: Comparison of outcome measures of sleepiness (the paired T-test) after the three types of intervention with the Placebo condition

Outcome measure	Type of intervention	Placebo		Intervention		Paired differences between the Placebo condition and the 3 types of interventions				t	DF	Sig. (2-tailed)
								95% Confidence Interval of the Difference				
		Mean	SD	Mean	SD	Mean	SD	Lower	Upper			
SD of EEG alpha power (mV^2)	Light alone	4.11	4.46	3.25	3.09	0.86	2.98	-0.24	1.97	1.58	29	0.123
	Caffeine alone	3.36	3.32	2.4	2.52	0.96	2.5	0.02	1.89	2.1	29	0.044*
	Light and Caffeine in combination	4.44	5.74	3.03	2.68	1.41	5.44	-0.61	3.44	1.42	29	0.16
Mean RR (milliseconds)	Light alone	849.14	107.38	1010.8	690.11	-161.73	700.28	-438.75	115.28	-1.2	26	0.241
	Caffeine alone	860	95.15	955	260.62	-95.01	225.29	-184.13	-5.89	-2.19	26	0.038*
	Light and Caffeine in combination	877.2	100.72	930	102.57	-52.77	43.04	-71.38	-34.15	-5.88	22	0.001*
Mean HR (beats/minute)	Light alone	72.27	9.05	70.82	10.02	1.45	5.18	-0.593	3.5	1.46	26	0.156
	Caffeine alone	71.06	7.55	67.12	8	3.94	3.65	2.49	5.39	5.6	26	.0001*
	Light and Caffeine in combination	69.77	7.45	65.76	7.04	4.01	3.1	2.66	5.35	6.19	22	.0001*
KSS	Light alone	6.23	2.11	5.33	2.12	0.9	1.76	0.23	1.56	2.78	29	0.009*

Outcome measure	Type of intervention	Placebo		Intervention		Paired differences between the Placebo condition and the 3 types of interventions				t	DF	Sig. (2-tailed)
Percentage of lapses (%)	Caffeine alone	6.2	2.39	5.23	2.3	0.96	1.351	0.46	1.471	3.91	29	0.001*
	Light and Caffeine in combination	5.9	2.18	4.36	2.12	1.53	1.94	0.8	2.25	4.32	29	0.001*
	Light alone	24.6	26.87	18.11	21.52	6.491	19.49	-0.78	13.77	1.82	29	0.079
	Caffeine alone	21.7	25.25	15.45	21.55	6.25	13.93	1.04	11.45	2.45	29	0.02*
	Light and Caffeine in combination	19.19	22.72	12.31	18.08	6.88	14.03	1.64	12.12	2.68	29	0.012*
Percentage of correct responses	Light alone	73.45	27.7	80.4	21.3	-6.94	19.64	-14.28	0.39	-1.93	29	0.063
	Caffeine alone	77.3	25.61	83.48	21.53	-6.17	14.32	-11.52	-0.82	-2.36	29	0.025*
	Light and Caffeine in combination	79.45	22.8	86.43	18.45	-6.97	14.82	-12.51	-1.43	-2.57	29	0.015*
Mean of the slowest 10% of 1/RTs (s^{-1})	Light alone	2.19	0.455	2.28	0.22	-0.09	0.49	-0.28	0.09	-1.04	29	0.307
	Caffeine alone	2.19	0.466	2.32	0.57	-0.12	0.32	-0.248	0	-2.19	29	0.036*
	Light and Caffeine in combination	2.17	0.547	2.32	0.225	-0.14	0.5	-0.33	0.04	-1.6	29	0.12
Mean reciprocals of correct responses and lapses (s^{-1})	Light alone	2.66	0.636	2.63	0.74	0.03	0.58	-0.18	0.25	0.3	29	0.766
	Caffeine alone	2.69	0.673	2.83	0.61	-0.13	0.37	-0.27	0	-1.97	29	0.058
	Light and Caffeine in combination	2.76	0.611	2.94	0.55	-0.17	0.35	-0.3	-0.04	-2.74	29	0.01*

Outcome measure	Type of intervention	Placebo		Intervention		Paired differences between the Placebo condition and the 3 types of interventions				t	DF	Sig. (2-tailed)
Absolute value of lateral acceleration (m/s^2)	Light alone	0.19	0.19	0.16	0.12	0.03	0.11	0	0.08	1.75	28	0.09
	Caffeine alone	0.17	0.13	0.12	0.08	0.05	0.08	0.02	0.08	3.34	29	0.002*
	Light and Caffeine in combination	0.23	0.24	0.16	0.17	0.07	0.13	0.02	0.12	2.99	29	0.006*
Absolute value of steering wheel angle (degree)	Light alone	1.01	0.88	0.78	0.52	0.22	0.57	0	0.44	2.1	28	0.044*
	Caffeine alone	0.91	0.6	0.64	0.35	0.27	0.43	0.11	0.43	3.44	29	0.002*
	Light and Caffeine in combination	1.27	1.19	0.84	0.83	0.42	0.71	0.15	0.69	3.24	29	0.003*
SD of lateral lane position	Light alone	0.57	0.2	1.03	2.53	-0.46	2.52	-1.42	0.49	-0.99	28	0.33
	Caffeine alone	0.61	0.28	0.53	0.19	0.07	0.23	-0.01	0.16	1.78	29	0.084
	Light and Caffeine in combination	0.69	0.35	0.55	0.18	0.14	0.25	0.04	0.23	3.05	29	0.005*
Total number of collisions	Light alone	3.7	8.58	0	0	3.7	8.58	0.49	6.9	2.36	29	0.025*
	Caffeine alone	3.66	13.81	2.03	5.18	1.63	12.84	-3.16	6.43	0.69	29	0.492
	Light and Caffeine in combination	4.03	9.32	4.13	8.36	-0.1	10.331	-3.95	3.75	-0.05	29	0.958
Total number of road edge	Light alone	20.56	32.94	17	23.51	3.56	16.61	-2.63	9.77	1.17	29	0.249
	Caffeine alone	18.56	25.4	10.36	12.54	8.2	16.67	1.97	14.42	2.69	29	0.012*

Outcome measure	Type of intervention	Placebo		Intervention		Paired differences between the Placebo condition and the 3 types of interventions				t	DF	Sig. (2-tailed)
excursions	Light and Caffeine in combination	25	33.99	16.66	20.21	8.33	19.47	1.06	15.6	2.34	29	0.026*
Total number of off-road crash	Light alone	18	36.42	16.13	26.9	1.86	15.54	-3.93	7.66	0.65	29	0.516
	Caffeine alone	18.1	29.99	11.23	15.94	6.86	17.67	0.26	13.46	2.12	29	0.042*
	Light and Caffeine in combination	14.56	21.13	10.6	15.72	3.96	12.11	-0.55	8.491	1.79	29	0.083
Total number of speed exceedances	Light alone	13.06	9.221	10.56	8.33	2.5	4.78	0.71	4.28	2.86	29	0.008*
	Caffeine alone	10.6	6.371	8.6	5.6	2	5.43	-0.02	4.02	2.01	29	0.053
	Light and Caffeine in combination	9.56	8.228	9.3	7.26	0.26	6.02	-1.98	2.51	0.24	29	0.81

RR = beat-to-beat interval, HR = heart rate,

SD = Standard deviation, DF = Degree of freedom

* $p < 0.05$

Table 6.9 Pairwise comparisons of outcome measures of sleepiness for the two factors "Type of intervention" and "Placebo vs Intervention"

Variable	Factor	Pairs		Mean Difference	P-value	Lower Bound	Upper Bound
SD of EEG alpha power (mV^2)	Type of intervention	1	2	0.05	1	-1.07	1.19
			3	0.85	0.12	-0.16	1.87
		2	3	0.79	0.252	-0.33	1.92
	Placebo vs Intervention	1	2	1.08	0.047*	0.01	2.14
Mean RR (millisecond)	Type of intervention	1	2	45.76	0.001*	17.14	74.38
			3	-13.27	1	-91.26	64.70
		2	3	-59.04	0.14	-131.66	13.57
	Placebo vs Intervention	1	2	-61.05	0.003*	-99.37	-22.73
Mean HR (beats/minute)	Type of intervention	1	2	-3.85	0.001*	-6.10	-1.59
			3	-0.86	1	-3.83	2.10
		2	3	2.98	0.138	-0.67	6.64
	Placebo vs Intervention	1	2	3.49	0.001*	2.44	4.54
LF/HF	Type of intervention	1	2	-.526	0.027*	-1.00	-0.05
			3	-1.19	0.706	-3.73	1.34
		2	3	-0.67	1	-3.51	2.17
	Placebo vs Intervention	1	2	-0.33	0.521	-1.40	0.73
KSS	Type of intervention	1	2	-0.65	0.025*	-1.34	0.04
			3	-0.58	0.051*	-1.31	0.14
		2	3	0.06	0.789	-0.56	0.69

Variable	Factor	Pairs		Mean Difference	P-value	Lower Bound	Upper Bound
Percentage of lapses (%)	Placebo vs Intervention	1	2	1.13	0.001*	0.66	1.60
	Type of intervention	1	2	-5.60	0.044*	-11	-0.11
			3	-2.82	0.65	-8.5	2.85
		2	3	2.78	0.291	-1.3	6.91
Percentage of correct responses (%)	Placebo vs Intervention	1	2	6.54	0.004*	2.21	10.88
	Type of intervention	1	2	6.01	0.041*	0.2	11.82
			3	2.55	0.825	-3.3	8.38
		2	3	-3.46	0.16	-7.8	0.90
Mean of the slowest 10% of 1/RT(1/S)	Placebo vs Intervention	1	2	-6.70	0.004*	-11	-2.28
	Type of intervention	1	2	0.01	1	-0.08	0.11
			3	-0.00	1	-0.13	0.12
		2	3	-0.02	1	-0.17	0.13
Mean reciprocals of correct responses and lapses	Placebo vs Intervention	1	2	-.12	0.036*	-0.24	-0.00
	Type of intervention	1	2	.20	0.028*	0.02	0.39
			3	0.09	0.242	-0	0.21
		2	3	-0.11	0.206	-0.3	0.04
Absolute value of lateral acceleration	Placebo vs Intervention	1	2	-0.09	0.12	-0.21	0.02
	Type of intervention	1	2	0.02	0.689	-0.02	0.07
			3	0.05	0.083	-0.00	0.11
		2	3	0.03	0.13	-0.00	0.06

Variable	Factor	Pairs		Mean Difference	P-value	Lower Bound	Upper Bound
Absolute value of steering wheel angle (degree)	Placebo vs Intervention	1	2	.054	0.002*	0.02	0.08
	Type of intervention	1	2	0.17	0.119	-0.04	0.38
			3	0.3	0.023*	0.045	0.54
		2	3	0.12	0.095	-0.02	0.27
	Placebo vs Intervention	1	2	.309	0*	0.15	0.46
SD of lateral lane position	Type of intervention	1	2	-0.17	1	-0.8	0.44
			3	0.05	0.32	-0.02	0.14
		2	3	0.23	0.996	-0.36	0.83
	Placebo vs Intervention	1	2	-0.07	0.618	-0.4	0.24
Total number of collisions	Type of intervention	1	2	2.23	0.098	-0.29	4.76
			3	1.23	1	-2.96	5.42
		2	3	-1	1	-5.43	3.43
	Placebo vs Intervention	1	2	1.74	0.16	-0.73	4.21
Total number of road edge excursions	Type of intervention	1	2	2.05	0.344	-2.30	6.40
			3	6.36	0.024*	0.92	11.81
		2	3	4.31	0.074	-0.43	9.07
	Placebo vs Intervention	1	2	6.70	0.013*	1.50	11.89
Total number of off-road crash	Type of intervention	1	2	-4.48	1	-22.13	13.16
			3	-2.08	1	-16.03	11.87
		2	3	2.4	1	-6.39	11.19
	Placebo vs Intervention	1	2	4.23	0.024*	0.61	7.85

Variable	Factor	Pairs		Mean Difference	P-value	Lower Bound	Upper Bound
Total number of speed exceedances	Type of intervention	1	2	-2.38	0.031*	-4.52	-0.23
			3	-0.16	0.858	-2.05	1.72
		2	3	2.21	0.046*	0.03	4.39
	Placebo vs Intervention	1	2	1.58	0.042*	0.05	3.11

1 = Light and caffeine in combination, 2 = Light alone, 3 = Caffeine alone, RR = beat-to-beat interval, HR = heart rate,

SD =Standard deviation,

*$p < 0.05$

6.2.2 Hypothesis 1: Light (condition 2) has an alerting effect relative to the Placebo condition (condition 4)

Main effect of light alone on objective outcome measures of sleepiness

Findings from the 2 x 3 ANOVA (Table 6.7) showed that there was a main effect of the factor "Placebo Vs Intervention" on three primary outcomes: the standard deviation of EEG alpha power ($F_{1, 29} = 4.324$, $p = 0.047$, partial $\eta^2 = 0.130$, power = 0.520), the ECG-based outcomes of mean RR ($F_{1, 22} = 10.91$, $p = 0.003$, partial $\eta^2 = 0.33$, power = 0.88), and mean HR ($F_{1, 22} = 47.42$, $p = 0.001$, partial $\eta^2 = 0.68$, power = 1). These effects represent a medium effect size on the standard deviation of EEG alpha power, and large effect sizes on both mean RR and mean HR based on effect size conventions for partial η^2 (Watson et al., 2015). Subsequent paired T-tests showed that the mean differences in the standard deviation of EEG alpha power (0.86), mean RR (-161.73 milliseconds) and mean HR (1.45 beats/minute) between light alone and the Placebo condition were not significant ($p = 0.123$, $p = 0.241$, $p = 0.156$, respectively). Therefore, light alone had no alerting effect on either EEG or ECG-related sleepiness outcome measures.

For the PPVT-related sleepiness outcome measures there was a main effect of the factor "Placebo vs Intervention" (Table 6.7) for the percentage of lapses ($F_{1, 29} = 9.524$, $p = 0.004$, partial $\eta^2 = 0.242$, power = 0.847), percentage of correct responses ($F_{1, 29} = 9.642$, $p = 0.004$, partial $\eta^2 = 0.250$, power = 0.851), and mean of the slowest 10% of 1/RTs ($F_{1, 29} = 4.819$, $p = 0.036$, partial $\eta^2 = 0.142$, power = 0.564). These are associated with a medium effect size on all PPVT outcome measures (Watson et al., 2015). However, the paired T-test showed that light alone did not significantly improve any of these outcome measures when compared with the Placebo condition ($p = 0.079$, $p = 0.063$, $p = 0.307$, respectively).

Overall, when compared with the Placebo condition, none of objective sleepiness outcome measures changed under light alone (condition 2). Therefore, these data *do not support* an alerting effect of light alone on objective sleepiness outcome measures.

Main effect of light alone on subjective outcome of sleepiness

There was a large effect of the factor "Placebo vs Intervention" (Watson et al., 2015) on subjective sleepiness, measured by Karolinska Sleepiness Scale (KSS; Table 6.7), when compared with the Placebo condition ($F_{1, 29}$ = 24.578, p = 0.001, partial η^2 = 0.459, power = 0.998). With regards to the specific effect of light alone, the paired T-test revealed that the mean sleepiness scores decreased significantly by 0.9 score points from a KSS score of 6.2 ('some signs of sleepiness') in the Placebo condition to a KSS score of 5.3 ('neither alert nor sleepy') after receiving the light alone (t_{29} = 3.91, p = 0.009). These results *support* the hypothesis of an alerting effect of light alone on subjective sleepiness.

Main effect of the light on the driving performance outcome measures of sleepiness

The analysis described in Table 6.7 showed the main effect of the factor "Placebo vs Intervention" on some driving performance outcome measures including the absolute value of lateral acceleration ($F_{1, 28}$ = 12.29, p = 0.002, partial η^2 = 0.30, power = 0.92), the absolute value of steering wheel angle ($F_{1, 28}$ = 16.91, p = 0.001, partial η^2 = 0.37, power = 0.97), total number of road edge excursions ($F_{1, 29}$ = 6.96, p = 0.013, partial η^2 = 0.19, power = 0.72), total number of off-road crashes ($F_{1, 29}$ = 5.70, p = 0.024, partial η^2 = 0.16, power = 0.63), and the total number of speed exceedances ($F_{1, 29}$ = 4.50, p = 0.042, partial η^2 = 0.13, power = 0.53). The effect sizes suggest a large effect of intervention on the absolute value of lateral acceleration and the absolute value of steering wheel angle, and a medium effect of intervention on the latter three variables.

The paired T-test showed that the absolute value of lateral acceleration dropped from 0.19 to 0.16 m/s^2. This drop of 0.03 m/s^2 was not significant after receiving light only when compared with the Placebo condition (p = 0.09). The absolute value of steering wheel angle had a significant drop of 0.22 degrees from 1.01 degrees in the Placebo condition to 0.78 degrees after receiving light alone (t_{28} = 2.10, p = 0.044). The total number of speed exceedances (Table 6.7) showed a significant change after the intervention ($F_{1, 29}$ = 4.508, p = 0.04, partial η^2 = 0.135, power = 0.537). Regarding the discrete effect of light alone, the paired T-test showed a significant reduction of

2.5 speed exceedances, from a mean of 13.06 under the Placebo condition to 10.56 after receiving the light alone *(*t_{29} = 2.86, *p* = 0.008). These findings *partly support* the hypothesis of an alerting effects of light alone on driving performance outcome measures, in that light alone improved some but not all driving performance outcome measures.

Taking the effects of light alone on all primary outcome measures of interest into account, these data *partly support* the hypothesis of an alerting effect of the light, in that light alone could improve subjective sleepiness and two driving performance outcome measures.

6.2.3 Hypothesis 2: Caffeine (condition 3) has an alerting effect compared to the Placebo condition (condition 4)

Main effect of caffeine on the objective outcomes of sleepiness

Of all the EEG-based outcome measures (Table 6.7), a medium effect of the "Intervention" was found only for the SD of EEG alpha power when compared to the Placebo condition ($F_{1, 29}$ = 4.324, p = 0.047, partial η^2 = 0.130, power = 0.520). The paired T-test revealed that the SD of EEG alpha power dropped significantly by 0.96 mV^2 from 3.36 mV^2 in the Placebo condition to 2.40 mV^2 after caffeine alone (t_{29} = 2.103, p = 0.044).

Of the ECG-based outcome measures, the factor "Placebo vs Intervention" had a large effect for change in the mean beat-to-beat intervals (mean RR) ($F_{1, 22}$ = 10.91, p = 0.003, partial η^2 = 0.33, power = 0.88). The Paired T-test revealed that mean RR increased significantly by 95 milliseconds, from a mean of 860 milliseconds in the Placebo condition to 955 milliseconds after caffeine alone (t_{29} = 2.19, p = 0.038). A large effect of the factor "Placebo vs Intervention" was also observed for change in mean heart rate ($F_{1, 22}$ = 47.42, p = 0.001, partial η^2 = 0.68, power = 1). The paired T-test showed that the mean HR had a significant decrease of 3.94 (beats/min), from 71.06 beats/min in the Placebo condition to 67.12 beats/min after receiving caffeine alone (t_{29} = 5.6, p = 0.001). In general, caffeine alone did not improve either the EEG or the ECG-related sleepiness outcome measures.

Of all the PPVT outcome measures, an overall medium effect (Watson et al., 2015) of the "Intervention" was found (Table 6.7) for all three outcome measures; the percentage of lapses ($F_{1, 29} = 9.524$, $p = 0.004$, partial $\eta^2 = 0.242$, power = 0.847), the percentage of correct responses ($F_{1, 29} = 9.642$, $p = 0.004$, partial $\eta^2 = 0.250$, power = 0.851), and the mean of the slowest 10% of 1/RTs as opposed to the Placebo condition ($F_{1, 29} = 4.819$, $p = 0.036$, partial $\eta^2 = 0.142$, power = 0.564). The paired T-test revealed that caffeine alone decreased the percentage of lapses to 15.4% (down from 21.7% under the placebo condition), a drop of 6.25% ($t_{29} = 2.45$, $p = 0.02$), and increased the percentage of correct responses by 6.17%, from 77.3% under the Placebo condition to 83.48%, ($t_{29} = 2.36$, $p = 0.025$). The paired T-test also showed that caffeine alone resulted in a rise of 0.12 (s^{-1}) in the mean of the slowest 10% of 1/RTs from 2.19 (s^{-1}) in the Placebo condition to 2.32 (s^{-1}) after the intervention ($t_{29} = 2.19$, $p = 0.036$). These results show that caffeine alone considerably improved the majority of PPVT-related sleepiness outcome measures.

Overall, taking all sleepiness outcome measures in to account, these data *partly support* the hypothesis of an alerting effect of caffeine alone on the objective sleepiness outcome measures.

Main effect of caffeine alone on the subjective outcome measures of sleepiness

Subjective sleepiness scores had a significant decrease of 0.966 points from a KSS score of 6.2 ('some signs of sleepiness') in the Placebo condition to a KSS score of 5.2 ('neither alert nor sleepy') after receiving caffeine alone ($t_{29} = 3.91$, $p = 0.001$). These findings *support* the hypothesis of the alerting effect of caffeine alone on subjective sleepiness.

Main effect of caffeine alone on the driving performance outcome measures

There were large effects of the factor "Placebo vs Intervention" (Table 6.7) for differences in the absolute value of lateral acceleration and the absolute value of steering wheel angle, and a medium effect for differences in the total number of road edge excursions ($F_{1, 29} = 6.967$, $p = 0.013$, partial $\eta^2 = 0.194$, power = 0.723) and the total number of off road crashes ($F_{1, 29} = 5.709$, $p = 0.024$, partial $\eta^2 = 0.164$, power =

0.637). The total number of off-road crashes was defined as all instances in which the centre of the car exceeded the off-road buffer distance of 0.99 m.

The paired T-test showed that there was a significant reduction of 0.05 m/s^2 from 0.17 m/s^2 in the Placebo condition to 0.12 m/s^2 after receiving caffeine alone $t_{(29)} = 3.34$, $p = 0.002$. Caffeine alone also significantly reduced the steering wheel angle by 0.27 degrees, from 0.91 degrees in the Placebo condition to 0.64 degrees, $t_{(29)} = 3.44$, $p = .002$. A significant decreased of 8.2 excursions was observed in the total number of road edge excursions, dropping from 18.5 excursions in the Placebo condition down to 10.36 excursions, $t_{(29)} = 2.69$, $p = .012$. The paired T-test also revealed that the total number of off-road crashes decreased by 6.8 crashes, from 18.1 crashes in the Placebo condition to 11.23 after receiving caffeine alone $t_{(29)} = 2.12$, $p = .042$.

There was also a medium effect of the factor "Placebo vs Intervention" for differences in the total number of speed exceedances ($F_{1, 29} = 4.50$, $p = 0.042$, partial $\eta^2 = 0.13$, power = 0.53). Caffeine alone resulted in a reduction of 2 exceedances, from 10.6 cases in the Placebo condition to 8.6 cases ($t_{29} = 2.01$, $p = 0.053$). However, this effect was <u>not</u> significant. These findings imply that caffeine had an alerting effect on the driving performance outcome measures, in that caffeine alone reduced the lateral acceleration, the steering wheel angle, total number of road edge excursions and off-road accidents.

In summary, these findings *partly support* the hypothesis for an alerting effect of caffeine alone when compared to the Placebo condition. This is because alerting effects of caffeine alone were found for some objective sleepiness outcomes, for subjective sleepiness, and for some driving performance outcome measures.

6.2.4 Hypothesis 3: Light and caffeine in combination (condition 1) has an alerting effect compared to the Placebo condition (condition 4)

Main effect of light and caffeine in combination on the objective sleepiness outcome measures

There was main effect of the factor "Placebo vs Intervention" on EEG and ECG-related outcome measures with a medium effect for differences in the SD of EEG alpha power, and large effects for differences in both mean RR, and mean HR (Table 6.7). The paired T-test showed that the SD of EEG alpha power did not change after receiving light and caffeine in combination when compared with the Placebo condition ($p = 0.165$). However, mean RR had a significant rise of 52.7 milliseconds from 877.2 milliseconds in the Placebo condition to 930 milliseconds after administering light and caffeine in combination ($t_{24} = -5.88$, $p = 0.001$). Light and caffeine in combination significantly decreased mean HR by 4.1 beats/min, from 69.77 beats/min in the Placebo condition to 65.76 beats/min ($t_{24} = 6.19$, $p = 0.001$). For the PPVT outcome measures, the main effect of the factor "Placebo vs Intervention" was observed for differences in the percentage of lapses and percentage of correct responses. The paired T-test revealed that both percentage of lapses and percentage of correct responses changed after the light and caffeine in combination, with the percentage of correct responses being 6.97% more ($t_{29} = 2.57$, $p = 0.015$), and the percentage of lapses being 6.8% less than the Placebo condition ($t_{29} = 2.68$, $p = 0.012$).

These findings suggest that light and caffeine in combination could improve some PPVT-related sleepiness outcome measures.

Overall, the findings *partly support* the hypothesis of an alerting effect of light and caffeine in combination on objective sleepiness outcome measures.

Main effect of light and caffeine in combination on the subjective outcome of sleepiness

The paired T-test found that subjective sleepiness decreased from a mean KSS score of 5.9 ('some signs of sleepiness') in the Placebo condition to a mean KSS score of 4.4 ('rather alert') after administering light and caffeine in combination ($t_{29} = 4.32$, p

= 0.001). This *supports* the hypothesis of an alerting effect of light and caffeine in combination on subjective sleepiness.

Main effect of light and caffeine in combination on the driving performance outcome measures of sleepiness

The ANOVA results in Table 6.7 suggest large effects of the factor "Placebo vs Intervention" for differences in mean steering wheel angular rate (changes in steering wheel angle per second) ($F_{1, 29}$ = 2771.36, p = 0.001, partial η^2 = 0.99, power = 1.00), the absolute value of lateral acceleration, and the absolute value of steering wheel angle. The factor "Placebo vs Intervention" had a medium effect on the total number of road edge excursions (see Section 6.2.3). A significant drop of 0.07 m/s^2 was found in the absolute value of lateral acceleration from 0.23 m/s^2 in the Placebo condition to 0.16 m/s^2 after providing light and caffeine in combination (t_{29} = 2.99, p = 0.006). Light and caffeine in combination resulted in a significant drop of 0.42 degrees in the absolute value of steering wheel angle, from 1.27 degrees in the Placebo condition to 0.84 degrees after the intervention (t_{29} = 3.241, p = 0.003). The total number of road edge excursions also dropped from 25 cases in the Placebo condition to 20.2 cases after receiving the light and caffeine in combination, a reduction of 8.3 cases (t_{29} = 2.34, p = 0.026). Based on these results, the hypothesis of alerting effects of light and caffeine in combination on driving performance outcome measures is *partly supported*.

Overall, these findings *partly support* the alerting effects of light and caffeine in combination when compared to the Placebo condition.

6.2.5 **Hypothesis 4: Light and caffeine in combination (condition 1) has a greater alerting effect than either light or caffeine alone**

Comparison of alerting effect of light and caffeine in combination with either light alone or caffeine alone on objective outcomes of sleepiness

Based on the main effect of the factor "Placebo vs Intervention" on the standard deviation of EEG alpha power, the paired T-test suggested a significant difference in the standard deviation of EEG alpha power after receiving caffeine alone as opposed to the Placebo condition. The results of the 2 x 3 ANOVA (Table 6.7) showed that

there was no main effect of the factor “Intervention type” on the standard deviation of EEG alpha power (p = 0.094). This suggests no significant difference between the standard deviation of EEG alpha power after caffeine alone or after the other two types of interventions (light alone and light and caffeine in combination). Figure 6.2 presents the comparison of mean values of the standard deviation of EEG alpha power in the Placebo condition and the three types of intervention.

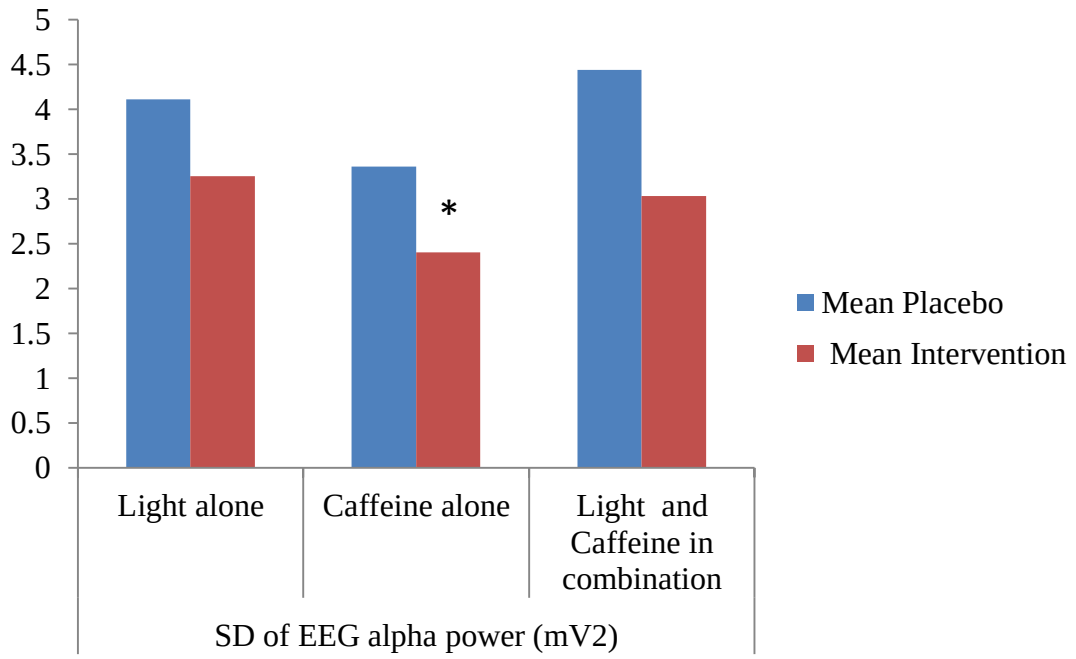

Figure 6.2. Comparison of the standard deviation of EEG alpha power in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

Based on the paired T-test both interventions of caffeine alone and light and caffeine in combination caused a significant rise in mean RR when compared with the Placebo conditions. The ANOVA (Table 6.7) did not suggest any within-subjects main effect of the factor “Intervention type” on this variable, however the Post-hoc T-test (Table 6.9) revealed that after receiving light and caffeine in combination, mean RR was 45 milliseconds more than after light only. Taking the more conservative within-subjects effect into account, the findings show no significant difference in mean RR between light and caffeine in combination and either caffeine

alone or light alone (p = 0.079). Figure 6.3 presents the differences in mean RR between the Placebo condition and the three types of intervention.

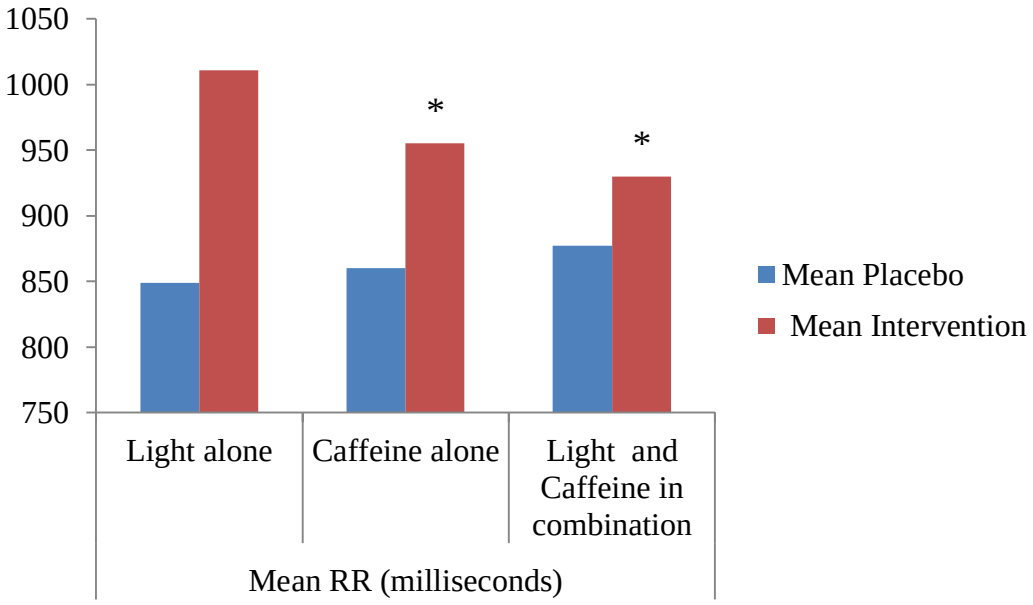

Figure 6.3. Differences between mean RR in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

The paired T-test revealed that the mean heart rate (Mean HR) significantly decreased after both interventions of caffeine alone and light and caffeine in combination by almost 4 beats/second as opposed to the Placebo conditions. The results of the ANOVA (Table 6.7) revealed a medium effect (Watson et al., 2015) of the "Intervention type" on this variable ($F_{1.66, 36.56} = 6.02$, p = 0.008, partial $\eta^2 = 0.21$, power = 0.80). According to the post-hoc T-test, the mean heart rate after light and caffeine in combination was 3.8 beats/min less than that of light alone (95% CI -6.10 to -1.59, p = 0.001). Figure 6.4 shows the differences of mean HR between the Placebo condition and the three types of intervention.

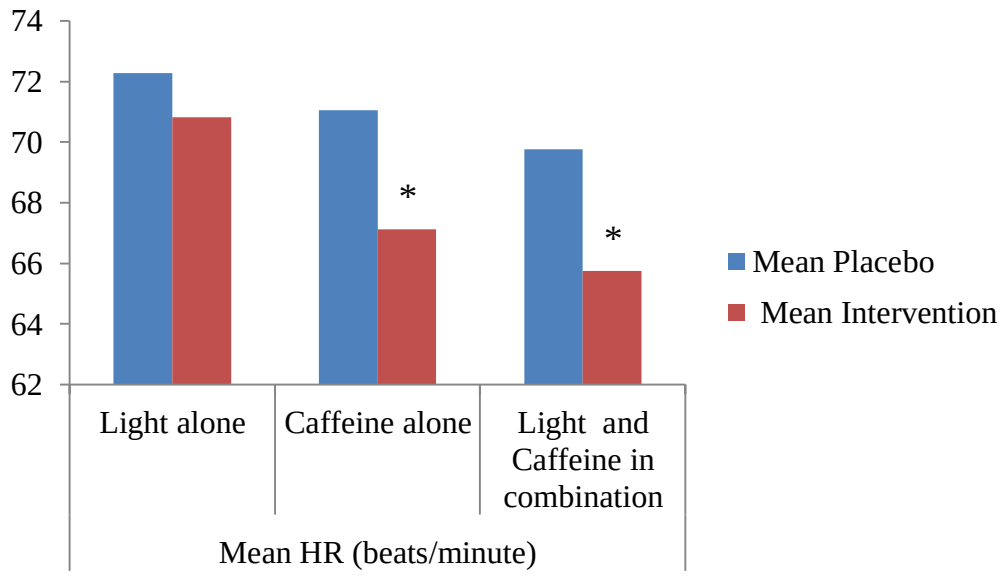

Figure 6.4. Differences in mean HRs between the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

Compared to the Placebo condition, both intervention types of caffeine alone and light and caffeine in combination resulted in a drop of more than 7% and 6% in the percentage of lapses, respectively. Based on the findings of the ANOVA (Table 6.7) there was also a medium effect (Watson et al., 2015) of the "Intervention type" on the percentage of lapses ($F_{2, 58} = 3.831$, $p = 0.027$, partial $\eta^2 = 0.117$, power = 0.673). The post-hoc T-test (Table 6.9) suggested that the percentage of lapses after receiving the light and caffeine in combination was 5.6% less than that of light alone (95% CI -11 to -0.113, $p = 0.044$). Figure 6.5 presents the differences of the percentage of lapses between the Placebo condition and the three types of intervention.

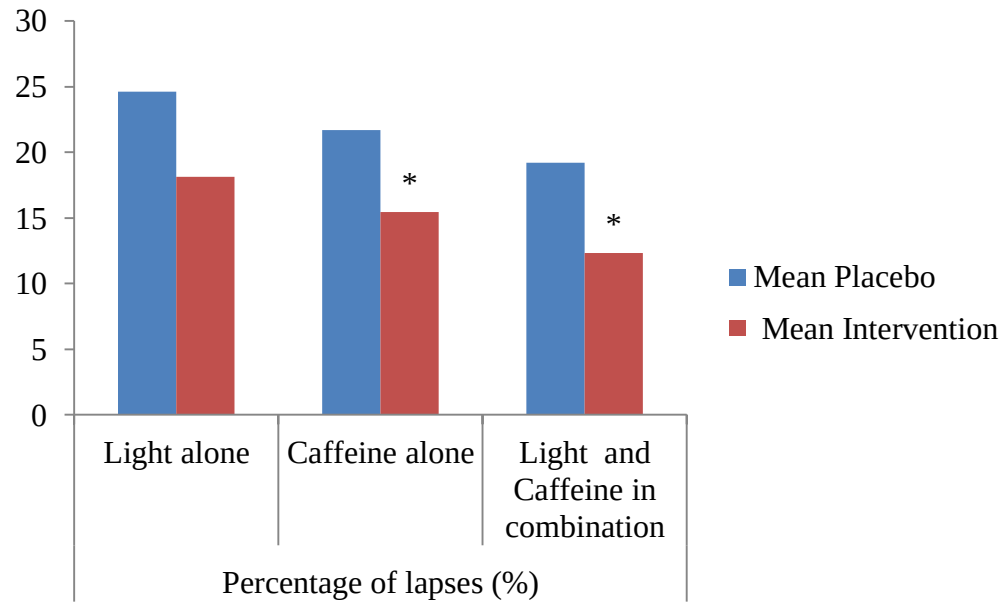

Figure 6.5. The differences between the percentage of lapses in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

The paired T-test revealed that compared to the Placebo condition, both interventions of caffeine alone and light and caffeine in combination significantly increased the percentage of correct responses by at least 6% and 7%, respectively. The analysis described in Table 6.7 showed that there was a small effect (Watson et al., 2015) of the "Intervention type" for differences in the percentage of correct responses ($F_{2, 58}$ = 4.064, p = 0.022, partial η^2 = 0.123, power = 0.701). Based on the post-hoc T-test (Table 6.9) the percentage of correct responses under the condition of the light and caffeine in combination was 6.05% greater than that of light alone (95% CI 0.2 to 11.22, p = 0.041). Figure 6.6 shows the differences between the percentage of correct responses in the Placebo condition and the three types of intervention.

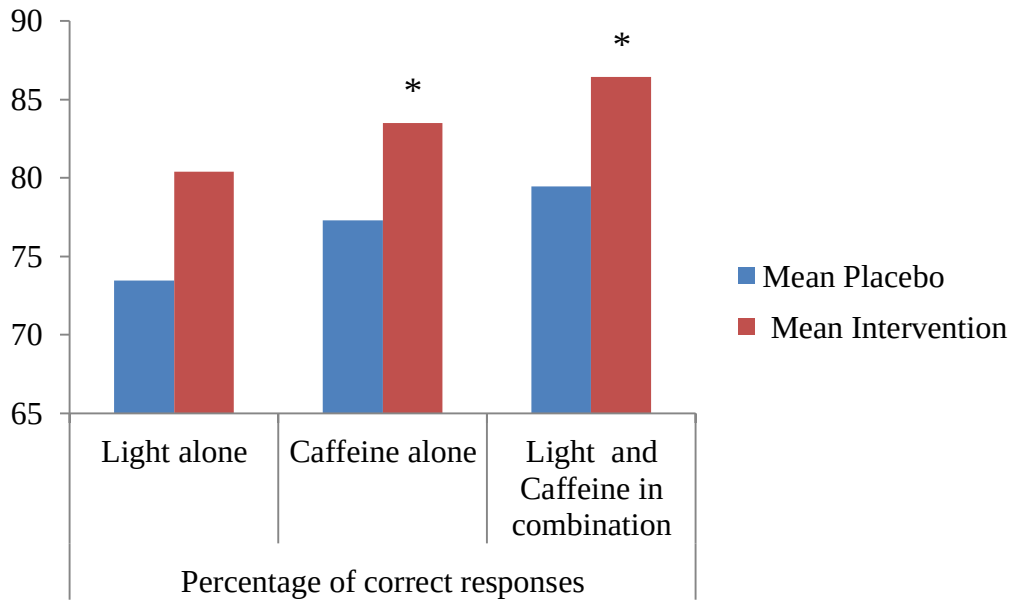

Figure 6.6. The differences between the percentage of correct responses in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

Of the three interventions types only caffeine alone could significantly increase the mean of the reciprocal of the slowest 10% RTs as opposed to the Placebo conditions. However, the ANOVA (Table 6.7) did not suggest any main effect of the "Intervention type" on this variable ($F_{1.759, 51.001} = 0.079$, $p = 0.904$, partial $\eta^2 = 0.003$, power = 0.601). The differences between the mean of the reciprocal of the slowest 10% RTs in the Placebo condition and the three types of interventions are presented in the Figure 6.7.

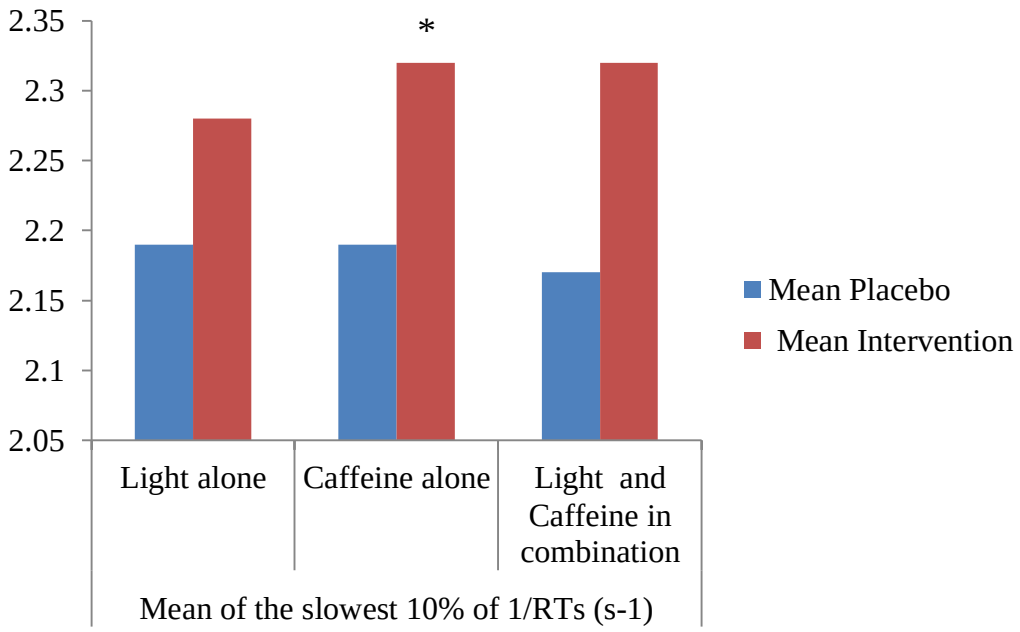

Figure 6.7. The differences between mean of the reciprocal of the slowest 10% RTs (s^{-1}) in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

According to results of the ANOVA (Table 6.7) there was no main effect of the factor "Placebo vs Intervention" on mean reciprocals of correct responses and lapses ($p = 0.12$), Nevertheless, there was a medium effect (Watson et al., 2015) of the "Intervention type" on this variable ($F_{1.763, 51.132} = 5.464$, $p = 0.009$, partial $\eta^2 = 0.159$, power = 0.793). The post-hoc T-test (Table 6.9) showed that the mean reciprocals of correct responses and lapses with light and caffeine in combination was 0.206 s^{-1} greater than for light alone (95% CI 0.02-0.395, $p = 0.028$). Figure 6.6 shows the differences between the mean reciprocals of correct responses and lapses in the Placebo condition and the three types of intervention.

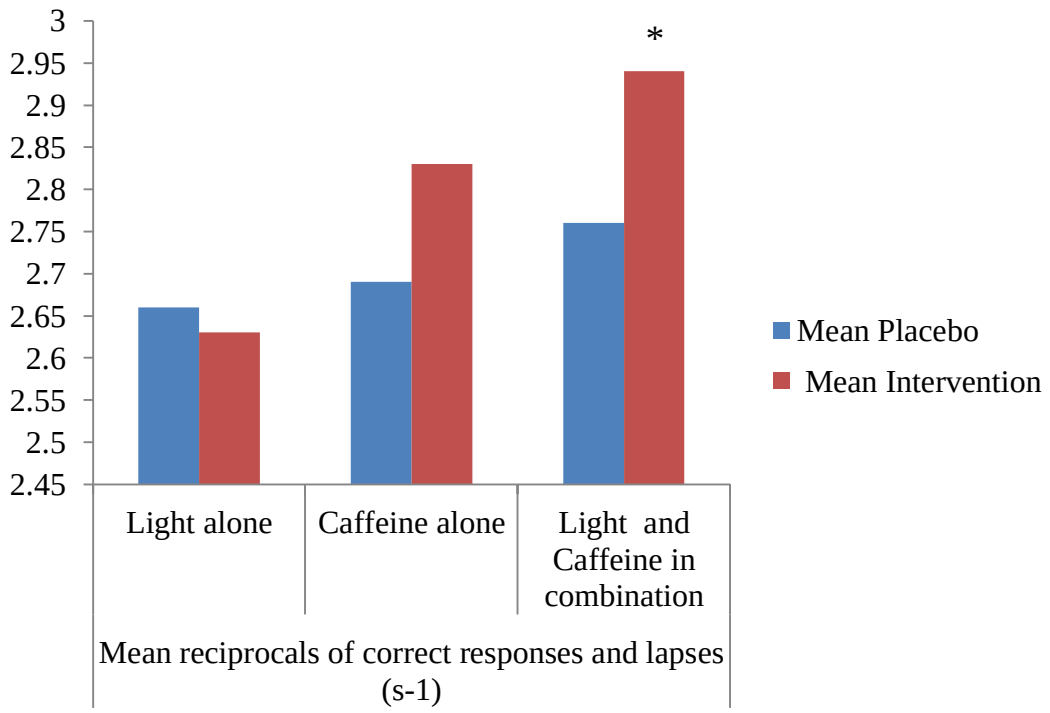

Figure 6.8. The differences between the mean reciprocals of correct responses and lapses in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

These results suggest that PPVT outcome measures improved after administering light and caffeine in combination more than with light alone. There was no difference between the effect of light and caffeine in combination and caffeine alone on PPVT.

Overall these data *partly support* the hypothesis of a greater alerting effect of light and caffeine in combination on objective sleepiness outcomes, when compared with either light alone or caffeine alone.

Comparison of alerting effect of light and caffeine in combination with either light alone or caffeine alone on subjective outcome of sleepiness

The paired T-test showed that both light alone and caffeine alone reduced subjective sleepiness from a KSS mean rating of 6 (‘some signs of sleepiness’) to a rating of 5 (‘neither alert nor sleepy’), while light and caffeine in combination decreased sleepiness ratings by 2 points to a rating of 4 (‘rather alert’). The ANOVA (Table 6.7) suggested that there was a small effect (Watson et al., 2015) of the “Intervention

type" on subjective sleepiness ($F_{2, 58}$ = 3.513, p = 0.036, partial η^2 = 0.108, power = 0.633). The post-hoc T-test revealed that light and caffeine in combination significantly reduced sleepiness scores by 0.65 points more than light alone (95% CI -1.348 to 0.048, p = 0.025), and by 0.58 points more than caffeine alone (95% CI -1.312 to 0.145; p = 0.051). Figure 6.9 represents the differences between mean subjective sleepiness with the Placebo condition and the three types of interventions.

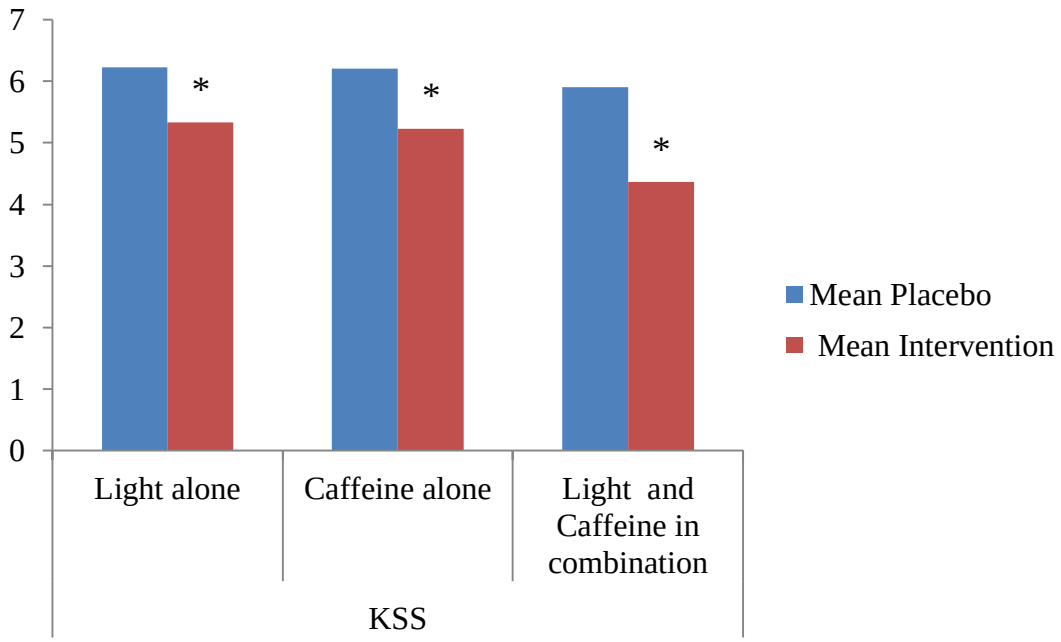

Figure 6.9. The differences between the mean KSS in the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

These results *support* the hypothesis that light and caffeine in combination has a greater alerting effect on subjective sleepiness than either light alone or caffeine alone.

Comparison of alerting effect of light and caffeine in combination with either light alone or caffeine alone on the driving performance outcome measures

Based on the 2-way ANOVA (Table 6.7) there was a small within-subjects effect (Watson et al., 2015) of the "Intervention type" on the absolute value of lateral

acceleration ($F_{1.65, 46.40}$ = 3.94, p = 0.033, partial η^2 = 0.12, power = 0.62). However, the Post-hoc T-test (Table 6.9) did not show any significant differences in this variable between light and caffeine in combination and either light alone (p = 0.689) or caffeine alone (p = 0.083). These data suggest no advantage of the three intervention types together. Figure 6.11 shows the differences in the absolute value of steering wheel angle with the Placebo condition and the three types of intervention.

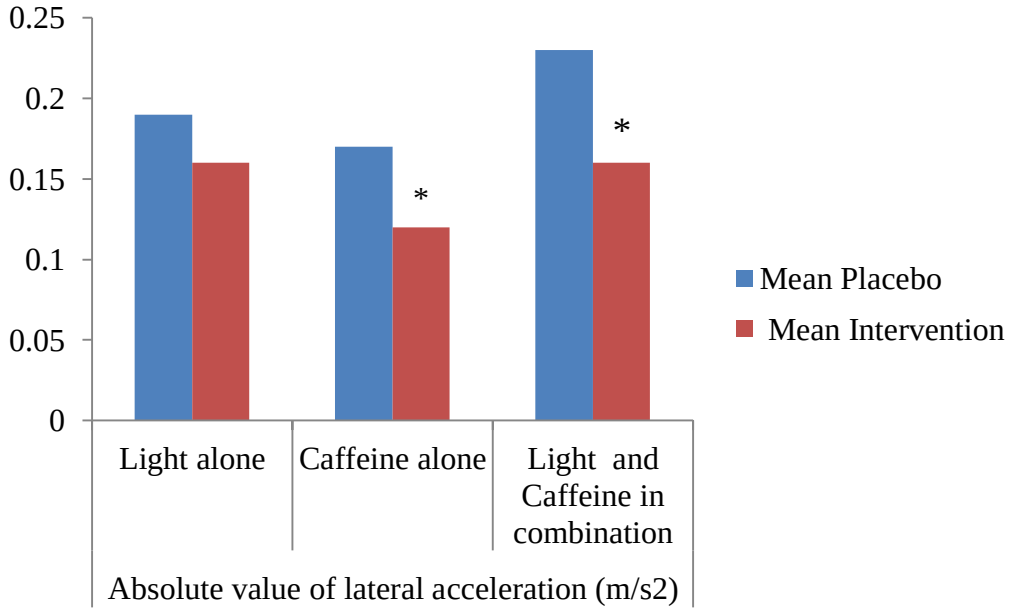

Figure 6.10 The differences of the absolute value of lateral acceleration (m/s^2) between the Placebo condition and the three types of intervention,*significant difference between the intervention and the Placebo condition

The 2-way ANOVA (Table 6.7) highlighted that there was a medium effect of the "Intervention type" on the absolute value of steering wheel angle ($F_{1.629, 45.618}$ = 4.198, p = 0.028, partial η^2 = 0.13, power = 0.649). The Post-hoc T-test revealed that the absolute value of steering wheel angle after administering light and caffeine in combination was almost 0.3 degrees more than that of caffeine alone (95% CI 0.045 to 0.549, p = 0.023), but not more than with light alone (p = 0.119). These data suggest that caffeine alone had a greater improving effect on this variable than did

light and caffeine in combination, but not more than light alone. Figure 6.11 shows the differences in the absolute value of steering wheel angle with the Placebo condition and the three types of intervention. In this figure the smaller values are represent the more alerting effect.

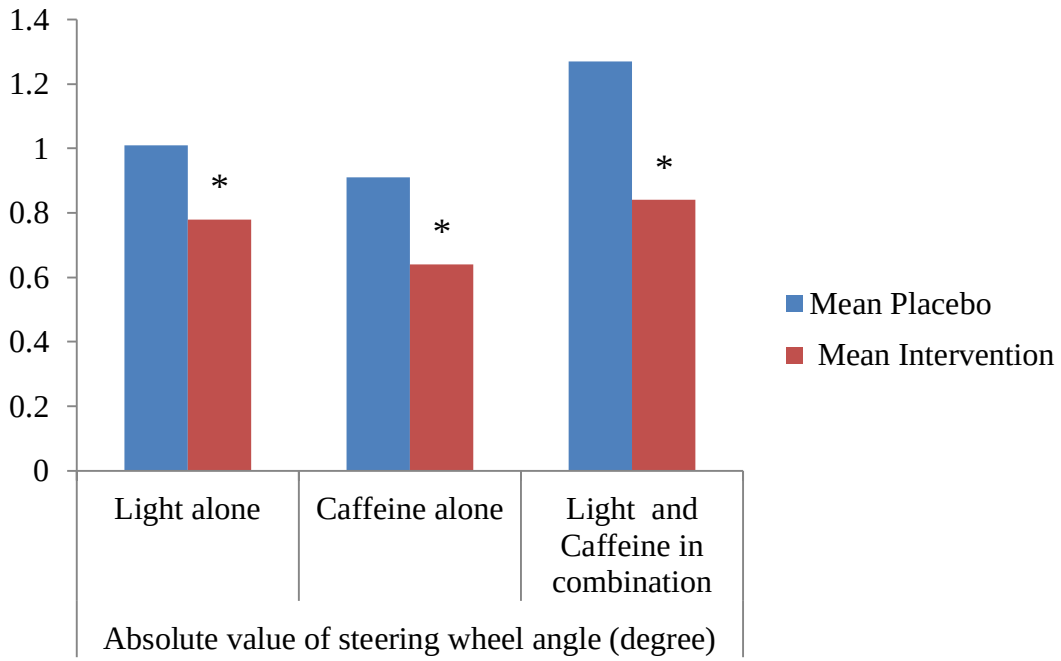

Figure 6.11. The differences the absolute value of steering wheel angle with the Placebo condition and the three types of intervention,*significant difference between the intervention and the Placebo condition

The paired T-test showed that the number of road edge excursions dropped significantly with both intervention types of light and caffeine in combination and caffeine alone when compared to the Placebo conditions. There was a medium effect of the "Intervention type" (Table 6.7) on the total number of road edge excursions ($F_{2, 58} = 3.721$, $p = 0.03$, partial $\eta^2 = 0.114$, power = 0.66). The Post-hoc T-test (Table 6.9) suggested that with light and caffeine in combination the number of road edge excursions was 6 cases more than with caffeine alone (95% CI 0.92 to 11.813, $p = 0.024$). There was no significant difference in this variable between light and caffeine in combination and light alone ($p = 0.344$), or between light alone and

caffeine alone (p = 0.07). These findings show that caffeine alone had a greater alerting effect than did light and caffeine in combination, and an effect equal to that of light alone. Figure 6.12 represents the differences in the total number of road edge excursions with the Placebo condition and the three types of intervention.

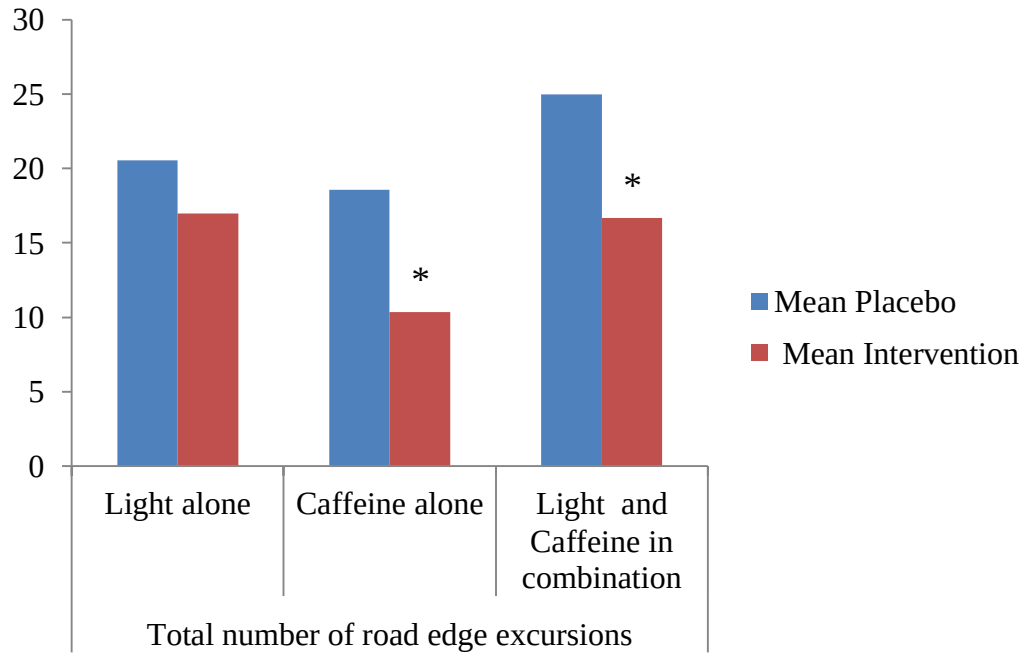

Figure 6.12. The differences of the total number of road edge excursions under the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

When compared with the Placebo condition, only caffeine alone reduced the total number of off-road crashes significantly (by about 7 crashes). Nevertheless, there was no main effect of the "Intervention type" (Table 6.7) on the total number of off-road crashes ($F_{1.349,\ 39.125}$ = 0.334, p = 0.632, partial η^2 = 0.011, power = 0.092). Based on the results of the Post-hoc T-test (Table 6.9), light and caffeine in combination did not significantly change this variable when compared to either light alone (p = 1.00), or to caffeine alone (p = 1.00). This suggests no advantage of light and caffeine in combination over either light alone or caffeine alone. Figure 6.13 represents the differences of the total number of off-road crashes under the Placebo condition and the three types of intervention.

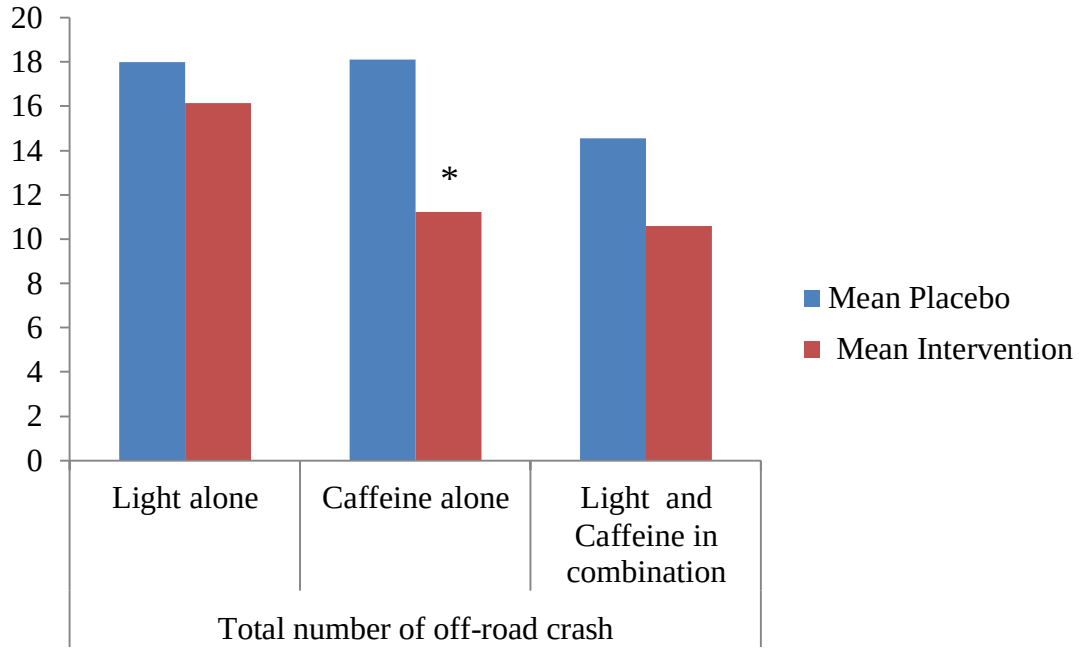

Figure 6.13. The differences of the total number of off- road crashes under the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

The paired T-test showed that, of the three intervention types, only the administration of light alone significantly reduced the number of speed exceedances when compared to the Placebo condition. The effect of caffeine alone ($p = 0.053$), as well as light and caffeine in combination ($p = 0.81$), were statistically insignificant. Based on the results of the ANOVA (Table 6.7) there was a small effect (Watson et al., 2015) of the factor "Intervention type" on the total number of speed exceedances ($F_{2, 58} = 3.444$, $p = 0.039$, partial $\eta^2 = 0.106$, power = 0.624). A further Post-hoc T-test showed that the number of speed exceedances after administering light alone was about 2.3 cases more than after light and caffeine in combination (95% CI -4.528 to -0.239, $p = 0.031$) and 2.2 cases more than after caffeine alone (95% CI 0.039 to 4.394, $p = 0.046$). However, this does not mean a lower alerting effect of light alone. As seen in Figure 6.14, even though the number of speed exceedances after receiving light alone is more than those of the other two interventions, the drop in this variable from the Placebo condition is greater with light alone when compared with the other two interventions. This indicates a greater alerting effect of light alone for the

number of speed exceedances than that of either caffeine alone or light and caffeine in combination. Figure 6.14 shows the differences in the total number of speed exceedances with the Placebo condition and the three types of intervention, with smaller values presenting a greater alerting effect.

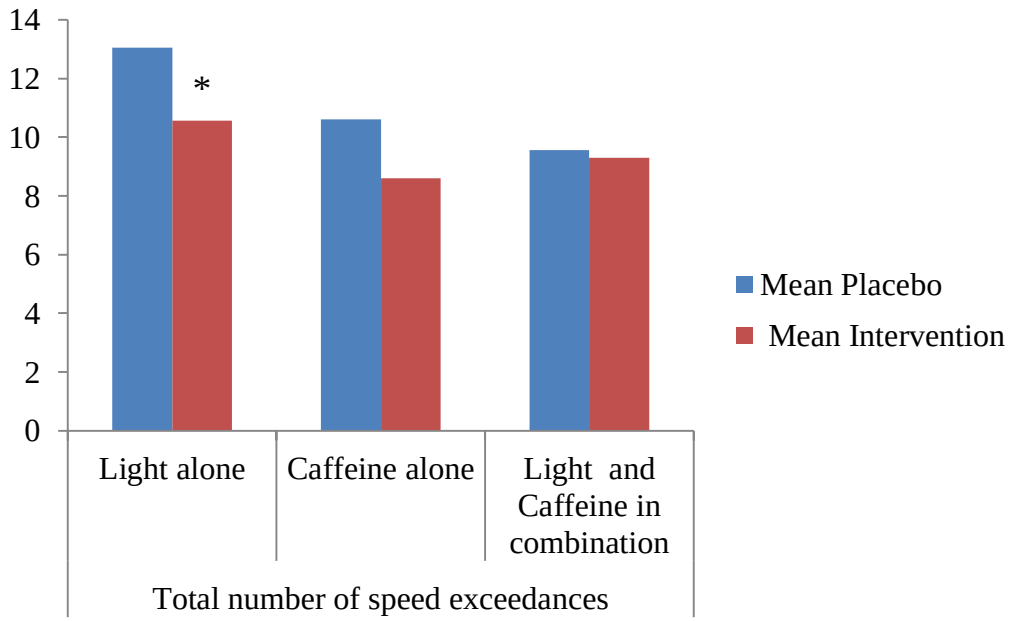

Figure 6.14. The differences of the total number of speed exceedances under the Placebo condition and the three types of intervention, *significant difference between the intervention and the Placebo condition

The results of the ANOVA *did not support* the hypothesis of greater effectiveness of light and caffeine in combination on driving performance outcome measures when compared with either light alone or caffeine alone. Taking all the findings together, these data *partly support* the hypothesis of the greater alerting effect of light and caffeine in combination than either light alone or caffeine alone.

6.2.6 **Hypothesis 5: Light alone has a greater alerting effect than caffeine alone**

The findings revealed that of all outcome measures, some EEG and ECG related measures remained unchanged by light alone but were impaired after consumption of caffeine. The majority of PPVT outcomes improved with caffeine alone, but remained unchanged after receiving light alone. A greater number of driving performance outcome measures improved with caffeine alone than with light alone.

Therefore, these data do not support the hypothesis of a greater alerting effect of light alone than caffeine alone (see Table 6.10 for summary).

Table 6.10 Summary of main effects of the two factors "Placebo vs Intervention" and "Intervention type" on primary-interest outcome measures

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
Objective sleepiness	SD of EEG alpha power (mV^2)	Main effect ($p = 0.047$, $\eta^2 = 0.13$)	Caffeine alone caused a decrease of 0.96 mV^2 (28%)	No main effect ($p = 0.225$)	light and caffeine in combination = Light alone = Caffeine alone
	Mean RR (milliseconds)	Main effect ($p = 0.003$, $\eta^2 = 0.33$)	Light and caffeine in combination caused an increase of 52.77 milliseconds (6%) Caffeine alone caused a 95.01 (11.04%) increase	No main effect ($p = 0.079$)	light and caffeine in combination = Light alone = Caffeine alone
	Mean HR (beats/minute)	Main effect ($p = 0.001$, $\eta^2 = 0.68$)	Light and caffeine in combination caused a decrease of 4.1beats/min (5%) Caffeine alone caused a 3.94 (5.5%)	*Main effect ($p = 0.008$, $\eta^2 = 0.21$)	Light alone > light and caffeine in combination 2-1 = 3.85 beats/min ($p = 0.001$) Light alone = Caffeine alone

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
			decrease		
	Percentage of lapses (%)	Main effect ($p = 0.004$, $\eta^2 = 0.24$)	Light and caffeine in combination, 7% decrease Caffeine alone caused a 6.25% decrease	*Main effect ($p = 0.027$, $\eta^2 = 0.117$)	light and caffeine in combination > Light, 1-2= -5.605 ($p = 0.044$), light and caffeine in combination = Caffeine alone ($p = 0.65$), Light alone= Caffeine alone ($p = 0.291$),
	Percentage of correct responses (%)	Main effect ($p = 0.004$, $\eta^2 = 0.25$)	light and caffeine in combination, 7% increase Caffeine alone caused a 6.17% increase	Main effect ($p = 0.022$, partial $\eta^2 = 0.123$)	light and caffeine in combination > Light alone, 1-2 = 6.015 ($p = 0.041$)

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
					light and caffeine in combination = Caffeine ($p = 0.825$), Light alone = Caffeine alone ($p = 0.16$),
	Mean of the slowest 10% of 1/RT (s^{-1})	Main effect ($p = 0.036$, $\eta^2 = 0.14$)	Caffeine alone caused a 0.12/s increase (5%)	No main effect ($p = 0.904$)	light and caffeine in combination = Light alone = Caffeine alone
	Mean reciprocals of correct responses and lapses (s^{-1})	No main effect ($p = 0.12$, $\eta^2 = 0.08$)		Main effect ($p = 0.009$, partial $\eta^2 = 0.159$)	light and caffeine in combination > Light alone, 1-2 = 0.206 ($p = 0.028$), Combination of light and caffeine = Caffeine alone,

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
					(p = 0.242), Light alone = Caffeine alone (p = 0.206),
Subjective sleepiness	KSS	Main effect (p = 0.001, η^2 = 0.45)	Light and caffeine in combination caused a decrease of 1.533 score in sleepiness rating Light alone, a decrease of 0.9 score Caffeine alone, a decrease of 0.966 score	Main effect (p = 0.036, η^2 = 0.108)	light and caffeine in combination > Light alone, 1^*-2 = -0.650 (p = 0.025), Light and caffeine in combination > Caffeine alone, 1-3= -0.583 (p = 0.051), Light alone = Caffeine alone (p = 0.789),

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
Driving performance	Absolute value of lateral acceleration (m/s^2)	Main effect ($p = 0.002$, $\eta^2 = 0.30$)	Caffeine alone, a decrease of 0.05 (m/s^2) Light and Caffeine in combination, a decrease of 0.07 (m/s^2)	Main effect ($p = 0.033$, $\eta^2 = 0.12$)	No difference was detectable; light and caffeine in combination = Light alone = Caffeine alone
	Absolute value of steering wheel angle (degree)	Main effect ($p = 0.001$, $\eta^2 = 0.37$)	Light and caffeine in combination caused a decrease of 0.42 degrees (33%) Light alone caused a decrease of 0.22 degrees (22%) Caffeine alone caused a decrease of 0.27 degree (30%)	Main effect ($p = 0.028$, partial $\eta^2 = 0.13$)	Light and caffeine in combination > Caffeine alone, 1-3 = 0.297 ($p = 0.023$), Light and caffeine in combination = Light alone = Caffeine alone ($p = 0.119$), Light alone = Caffeine

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
					alone (p = 0.095),
	Total number of road edge excursions	Main effect (p = 0.013, η^2 = 0.19)	Light and caffeine in combination cause a decrease of 8.3 cases (33%)	Main effect (p = 0.03, partial η^2 = 0.114)	Light and caffeine in combination > Caffeine alone, 1-3 = 6.36 (p = 0.024),
			Caffeine alone cause a decrease of 8.2 excursions (30%)		
	Total number of off-road crash	Main effect (p = 0.024, η^2 = 0.16)	Caffeine alone caused a decrease of 6.8 crashes (37%)	No main effect (p = 0.632)	Light and caffeine in combination = Light alone = Caffeine alone

Construct	Outcome	Main effect of the factor "Placebo vs Intervention" (**Table 6.7**)	The paired T-test (**Table 6.7**)	Main effect of the factor "Intervention type" (**Table 6.7**)	The post-hoc T-test (**Table 6.9**)
	Total number of speed exceedances	Main effect ($p = 0.04$, $\eta^2 = 0.13$)	Light alone caused a decrease of 2.5 exceedances compared to Placebo (19%)	Main effect ($p = 0.039$, partial $\eta^2 = 0.106$)	Light alone> light and caffeine in combination, 1-2= -2.383 (p=0.031) Light alone> Caffeine alone, 2-3= 2.217 (p=0.046) Light and caffeine in combination = Caffeine alone, p=0.85

RR= beat-to-beat interval, HR= heart rate, SD=Standard deviation,

*1=condition 1 (light and caffeine in combination), 2= condition 2 (light alone), 3= condition 3 (caffeine alone)

*$p < 0.05$

6.2.7 **Hypothesis 6: Administration of any intervention has an alerting effect compared to the Placebo condition**

To test this hypothesis, the main effect of the factor "Placebo vs Intervention" on the objective, subjective and the driving performance outcome measures were examined (Table 6.7). In case of any main effect, a post-hoc T-test was performed to determine the significant differences between the intervention and the Placebo condition (Table 6.9). As previously mentioned, in this analysis the 'intervention' refers to the overall or combined effect of the three intervention types. Of EEG and ECG-related outcome measures there was a main effect of the factor "Placebo vs Intervention" (Table 6.7) only on the standard deviation of EEG alpha power, and on the mean RR and the mean HR. The post-hoc T-test (Table 6.9) suggested that after the intervention the standard deviation of EEG alpha power was 1.081 (mV^2) less than in the Placebo condition (95% CI 0.018 to 2.144, p = 0.047, Bonferroni adjusted), the mean RR was 61 milliseconds higher than the Placebo condition (95% CI 99.37 to 22.73, p = 0.003, Bonferroni adjusted) and the mean HR decreased by 3.5 beats/min as opposed to the Placebo condition (95% CI 2.44 to 4.54, p = 0.001, Bonferroni adjusted). These changes in the three variables indicated increased sleepiness. Therefore, the EEG and the ECG-related outcome measures were not improved by the administration of the intervention and in some cases even degraded.

The 2-way ANOVA (Table 6.7) revealed that all PPVT-related outcome measures were significantly changed by the intervention, except for the mean reciprocals of correct responses and lapses (p = 0.120). The Post-hoc T-test (Table 6.9) revealed that after the intervention the percentage of lapses had a decrease of 6.54% (95% CI 2.21 to 10.88, p = 0.004), the percentage of correct responses had an increase of 6.7% (95% CI -11 to -2.28, p = 0.004) and the mean slowest 10% of 1/RTs had an increase of 0.124 (95% CI -0.2 to -0.008, p = 0.036) compared to the Placebo condition. These results *partly support* the hypothesis of improved PPVT-related outcome measures after the intervention.

Overall, these data *partly support* an overall alerting effect from the intervention on objective sleepiness outcome measures when compared with the placebo condition.

The findings of the ANOVA reflected in Table 6.7 showed that after the intervention KSS ratings decreased by an average of 1.133 points (95% CI 0.666 to 1.601, p = 0.001). This *supports* the hypothesis of an alerting effect of the intervention on subjective sleepiness when compared with the Placebo condition.

The results of the ANOVA (Table 6.7) showed a main effect of the factor "Placebo vs Intervention" on all driving performance outcome measures, except for the two variables of the standard deviation of lateral lane position (p = 0.617) and the total number of collisions (p = 0.160). The post-hoc T-test (Table 6.9) suggested that, when compared to the Placebo condition, the absolute value of lateral acceleration had a significant drop of 0.54 m/s^2 (95% CI 0.02 to 0.08, p = 0.002), the absolute value of steering wheel angle had a significant drop of 0.309 degrees (95% CI 0.155 to 0.462, p = 0.001), the number of speed exceedances had a decrease of 1.58 exceedances (95% CI 0.058 to 3.119, p = 0.042), the number of road edge excursions had a drop of 6.7 cases (95% CI 1.509 to 11.891, p = 0.013) and the total number of off-road crashes had a drop of 4.233 crashes (95% CI 0.61 to 7.857, p = 0.024) after the intervention. Therefore, these data *partly support* the hypothesis of an alerting effect of the intervention on driving performance outcome measures when compared to the Placebo condition.

Taking all data together, these results *partly support* the hypothesis of an alerting effect of the intervention when compared to the Placebo condition.

Chapter 7: Discussion

An overview of the whole program of research is provided in Section 7.1. The results are summarised in Section 7.1.3, followed by an interpretation of the findings in Section 7.2. The findings of the experimental study are compared and contrasted against findings from the reviewed literature in Section 7.3, followed by a description of the contribution of this research to existing knowledge in Section 7.4. Finally, some considerations are presented in Section 7.5.

7.1 OVERVIEW OF THE WHOLE PROGRAM OF RESEARCH

7.1.1 **Purpose/scope**

The purpose of this experimental study was to investigate the effects of light (provided at a pragmatic dose and via a commercially-available delivery system) on young drivers' alertness and performance, and to compare these effects to those provided by caffeine, after chronic partial sleep deprivation in a simulated driving experiment.

7.1.2 **Rationale for selecting the outcomes**

In the experimental study a multi-level approach to the measurement of driver sleepiness was taken. Sleepiness was measured by objective, subjective, and driving performance outcome measures. The rationale for measuring the objective outcomes of brain activity, heart rate variability, and psychomotor performance outcomes, stemmed from the findings of the narrative review suggesting that the influence of sleepiness upon performance commences at an earlier point than the driver's own perception of that moment. Psychomotor vigilance is a critical component of drivers' cognitive performance, and the PVT remains a standardized and sensitive probe in sleep and circadian research. The systematic review pointed out that PVT reaction times could slow by 45% after one week chronic sleep loss in young drivers (Rupp et

al., 2004), and the use of the PVT allows some comparisons with previous studies. The outcome of subjective sleepiness was also of importance in that, even after a perception of increased sleepiness and impaired performance, young drivers mostly carry on their drive (and in some cases to the point of a crash). Additionally, the literature showed that there is a paucity of data regarding variation in the KSS in response to light during daytime hours (Hommes & Giménez, 2015). Finally, based on the systematic review, driving performance in the simulator was measured by outcomes identified as particularly sensitive to sleepiness and/or critical for safe driving, such as the standard deviation of lateral position and inappropriate line crossings, the steering wheel angle, and speed.

7.1.3 **The results of this program of research**

The findings of the primary narrative review (Chapter 2) revealed that the homeostatic and circadian sleep drives are the two primary regulators of sleepiness, but their influence can be shaped by other contributing factors such as the presence of sleep disorders, time-on-task fatigue, consumption of drugs and medicines, and other sources of inter-individual differences. The primary narrative review also showed that young drivers are overrepresented in sleep-related crashes, and are more vulnerable to the devastating consequences of sleep loss. In order to have a better understanding of the effects of sleep loss on young drivers a systematic review (Chapter 3) was conducted. The systematic review revealed that between 2004 and 2014 only 10 studies were published on the effects of sleep loss on young drivers' performance. There were no standard outcome metrics or randomised control trial interventions for the problem of sleepy driving identified. The systematic review also found that about half the studies adopted samples of fewer than 15 participants, predominantly included only male drivers. Half of them were conducted during night time with acute sleep loss, and only one-fifth of studies adopted a chronic sleep deprivation paradigm. An equal number of studies objectively monitored and quantified the sleep manipulation by Actigraphy or by measuring wake EEG during their experiment. The majority of studies were undertaken on some sort of driving simulator. These properties have impacted the quality of evidence in this field and limit the generalizability of this evidence.

The process of developing the GRADE criteria for rating the quality of papers found that the most important degrading factor for the quality of papers was the risk of bias (mostly because of some flaws in the implementation of the study, such as inadequate monitoring of sleepiness during the test period and practice effects on the outcome measures used). The GRADE rating analysis revealed that this limited evidence on the effect of sleep loss on young drivers' performance was not a reliable source of information. The available evidence suffered from very low quality studies ($0 < OGS < 1$) for reaction time outcomes, and from low quality studies ($1 < OGS < 2$) for the standard deviation of lateral position. There is no high-quality evidence currently available on young drivers' performance after sleep loss.

In order to understand the effects of light and caffeine on young drivers' performance a second narrative review was performed (Chapter 4). The literature revealed that short wavelengths of light such as blue or green light have greater alerting effects than those of longer wavelengths such as yellow or white light of equivalent intensity. In parallel, caffeinated chewing gums have higher absorption rates than other forms of caffeine and even low doses of caffeine have alerting effects. However, the review showed that few studies have examined the alerting effects of either light or caffeine in the driving context. There were some specific gaps in the available literature; most studies have been conducted during the night time, and there was no clear evidence for an alerting effect of light and caffeine on young adults' objective and subjective sleepiness, or upon their driving performance, after chronic sleep loss during the daytime. These 'gaps' in the current literature were convincing enough to conduct an experimental driving study during the daytime hours (when young drivers typically experience mild sleepiness in their routine life and more often drive). The combined findings of the primary and secondary narrative reviews and the systematic review framed the structure of the experimental study including the study design, sample characteristics, outcomes and measurement tools. The experimental study (Chapter 5: and Chapter 6:) found that neither light, not caffeine alone, nor the combination of light and caffeine together improved the drivers' sleepiness outcomes on all objective, subjective, psychomotor performance, and driving performance measures. The data suggested that light and caffeine in combination could improve psychomotor performance (PPVT) outcomes to a greater extent than could light alone, but not to a greater extent than caffeine alone. Both

light and caffeine alone seemed to improve subjective sleepiness, while light and caffeine in combination had a greater alerting effect, with the drivers reporting themselves to be rather alert. Of the other primary outcomes, light alone improved speed exceedance and steering wheel angle indices, while caffeine alone or combined with light improved a broader range of outcomes including percentage of lapses, correct responses, steering wheel angle, and the total number of road edge excursions. However, these findings did not suggest any advantage for the combination light and caffeine over light alone, or over caffeine alone, in improving driving performance outcomes. Table 6.11 presents a summary of findings of the experimental study in terms of supporting the six primary hypotheses.

Table 6.11 Summary of findings of the experimental study and their overall support for the six primary hypotheses

Hypothesis	Description	Support of the hypothesis by objective, subjective and driving performance outcome measures of interest	Overall support for the hypothesis
Hypothesis 1	Light (condition 2) has an alerting effect relative to the Placebo condition (condition 4)	**Objective sleepiness outcomes** a. ***EEG outcomes***: Did not support b. ***ECG outcomes***: Did not support c. ***PPVT outcomes***: Did not support **Subjective sleepiness (KSS):** Supported **Driving performance outcomes:** Partly supported A decrease in the absolute value of steering wheel angle and speed exceedances.	*Partly supported*
Hypothesis 2	Caffeine (condition 3) has an alerting effect compared to the Placebo condition (condition 4)	**Objective sleepiness outcomes** a. ***EEG outcomes***: Did not support (even standard deviation of EEG alpha power decreased) b. ***ECG outcomes***: Did not support (even mean RR increased and mean HR decreased) c. ***PPVT outcomes***: Partly supported by reducing the percentage of lapses and increasing the percentage of correct responses and mean of the slowest 10% of 1/RTs. **Subjective sleepiness (KSS):** Supported **Driving performance outcomes:** Partly supported A decrease in the absolute	*Partly supported*

Hypothesis	Description	Support of the hypothesis by objective, subjective and driving performance outcome measures of interest	Overall support for the hypothesis
		value of lateral acceleration, the absolute value of steering wheel angle, total number of road edge excursions and total number of off-road crashes.	
Hypothesis 3	Light and caffeine in combination (condition 1) has an alerting effect compared to the Placebo condition (condition 4)	**Objective sleepiness outcomes** ***a.*** ***EEG outcomes:*** Did not support b. ***ECG outcomes:*** Did not support (even mean RR increased and mean HR decreased) **c.** ***PPVT outcomes:*** Partly supported by reducing the percentage of lapses and increasing the percentage of correct responses **d. Subjective sleepiness (KSS):** Supported **Driving performance outcomes**: Partly supported A decrease in the absolute value of lateral acceleration, the absolute value of steering wheel angle and total number of road edge excursions.	*Partly supported*
Hypothesis 4	Light and caffeine in combination (condition 1) has a greater alerting effect than either light or caffeine alone	**Objective sleepiness outcomes** ***a.*** ***EEG outcomes:*** Did not support e. ***ECG outcomes:*** Did not support (even mean HR was less than light alone) ***b.*** ***PPVT outcomes:*** Partly supported Percentage of lapses was less than that of light alone, percentage of	*Partly supported*

Hypothesis	Description	Support of the hypothesis by objective, subjective and driving performance outcome measures of interest	Overall support for the hypothesis
		correct responses was more than that of light alone, the mean reciprocals of correct responses and lapses was larger than that of light alone. **Subjective sleepiness (KSS):** Supported **Driving performance outcomes:** Did not support (Even the absolute value of steering wheel angle and the number of road edge excursions were both more than those of caffeine alone).	
Hypothesis 5	Light alone has a greater alerting effect than caffeine alone	**Objective sleepiness outcomes** ***a.*** ***EEG outcomes:*** Did not support ***b.*** ***ECG outcomes:*** Did not support ***c.*** ***PPVT outcomes:*** Did not support (the majority of PPVT outcomes improved by caffeine alone) **Subjective sleepiness (KSS):** Did not support **Driving performance outcomes Driving performance outcomes:** Did not support A decrease in the absolute value of lateral acceleration, total number of road edge excursions and total number of off-road crashes occurred by caffeine alone, but not after receiving light alone.	*Did not support*
Hypothesis 6	Administration of any intervention has an	**Objective sleepiness outcomes** ***a.*** ***EEG outcomes:*** Did not support (even standard deviation of EEG alpha	*Partly Supported*

Hypothesis	Description	Support of the hypothesis by objective, subjective and driving performance outcome measures of interest	Overall support for the hypothesis
	alerting effect compared to the Placebo condition	power decreased) ***b.*** ***ECG outcomes:*** Did not support (even mean RR increased and mean HR decreased) ***c.*** ***PPVT outcomes:*** Partly Supported All PPVT outcomes improved after the intervention except for the mean reciprocals of correct responses and lapses with no change. **Subjective sleepiness (KSS):** Supported **Driving performance outcomes**: Partly Supported All driving performance outcomes improved after the intervention except for the two variables of the standard deviation of lateral lane position and the total number of collisions with no changes.	

7.2 INTERPRETATION OF THE FINDINGS

In this experimental study participants' sleep-wake times were manipulated, and a chronic mild sleep loss was successfully induced.

A one-hour sleep loss was induced to simulate the sleep loss that is normally experienced by non-professional drivers and to have a more conservative estimate of the net effect of this limitation and potential benefits of interventional conditions. Based on the joint consensus statement of the American Academy of Sleep Medicine (AASM) and Sleep Research Society (ARS) sleep restricted to less than 7 hours per night is regarded as insufficient (Panel et al., 2015). This is a mild degree of sleep loss, consistent with that which might have result in mild levels of impairment and consequently the lower levels of improvements in sleepiness after administering the three conditions. Nevertheless, even a mild degree of sleepiness is not acceptable when driving. This degree of sleep restriction was enough to induce a subjective sleepiness level of 6, with effects observed on sensitive measures of specific aspects of neurocognitive function relevant to safe driving. A recent study shows that a rating of '6' or more on the KSS, is associated with impaired simulator driving performance and with increased real-world crash risk (Åkerstedt, Anund, Axelsson, & Kecklund, 2014). The one-hour sleep deprivation in this study did not induce progressive subjective sleepiness. This means that participants had the same subjective sleepiness at the beginning of each test day, and that the level of sleepiness did not vary considerably before administering the three conditions across the three test days.

As for the first hypothesis, the non-significant change in the objective sleepiness outcome measures after receiving light alone implies that the alerting effects of light were not sufficient to improve these outcomes. On the other hand, light alone did significantly improve the drivers' subjective sleepiness. This difference was sufficient to shift mean KSS scores from a value corresponding to "some signs of sleepiness" to value corresponding to "neither alert nor sleepy". One implication of this finding is a discrepancy or misalignment between subjective and objective sleepiness. This could mean that under such lighting condition drivers could perceive improved alertness and would keep driving, without any improvement in their

Light alone improved some driving performance outcome measures such as the absolute value of steering wheel angle and the total number of speed exceedances. Light alone decreased the absolute value of steering wheel angle by 0.2 degrees from 1.01 degrees in the Placebo condition to 0.78 degrees. These absolute values seem to be very small. However, as the simulator had a sensitive steering wheel, drivers were able to adjust the vehicle's lane position by small movements of the steering wheel. Therefore, the 0.2 degree corresponds to an attenuation of more than 20% in the magnitude of steering movements, and reflects better steering wheel control. Having a medium effect, light alone reduced the number of speed exceedances from 13 cases in the Placebo condition to 10.5 cases. This drop of 2 cases represents a one-fifth (19%) drop in speeding. However, more than 10 cases of speed exceedance remained. Overall, the light did not improve the drivers' alertness consistently across all levels of subjective sleepiness, objective sleepiness, and objective driving performance. Therefore, the first hypothesis is partly supported and provision of light alone could not be regarded as a reliable stimulant in the context of increased sleepiness.

The provision of caffeine did not improve any EEG-related outcome measures except for a decrease in the standard deviation of alpha power by 0.96 mV^2 from 3.3 mV^2. This is almost 30% attenuation in alpha power variability representing a medium effect of caffeine. Based on the classification of sleep onset period by Hori et al. (2001), increased alpha and theta EEG activity represent early stages of sleepiness. Therefore, this change represents less instability in alpha power and could be a sign of increased alertness. In contrast, caffeine alone did not improve ECG-related outcome measures, and did not prevent increasing mean heart beat-to-beat interval, and decreasing mean heart rate. Mean RR after consumption of caffeine rose by an average of 95 milliseconds (a decrease in mean heart rate by 4 beats/min). Since slower mean beat-to-beat intervals have been reported to reflect increased alertness (Rodriguez-Ibañez, García-Gonzalez, de la Cruz, Fernández-Chimeno, & Ramos-Castro, 2012), the increased mean RR and decreased HR in this study could be interpreted as increased sleepiness. However, that interpretation is contradicted by the parallel findings that caffeine alone improved the majority of PPVT outcome measures. Caffeine reduced the percentage of PPVT lapses and increased the percentage of correct responses by 6%. In addition, caffeine increased the mean

slowest 10% reciprocal of reaction times by 0.12/s. Given that higher values of mean of the slowest 10% of reciprocals of reaction times reflect higher reaction speeds (Loh et al., 2004; Sforza et al., 2004), these findings all imply that caffeine is able to decrease the proportion of slow reaction times and increase the reaction speed significantly. In spite of the medium effect of the intervention on above-mentioned three variables, lapses were still observed at a rate of 15% after consumption of caffeine.

Caffeine was also associated with a modest improvement in subjective sleepiness scores, shifting mean KSS scores from a value corresponding to "some signs of sleepiness" to value corresponding to "neither alert nor sleepy". This means that after consumption of caffeine, the feeling of *sleepiness* could disappear.

Caffeine was found to decrease the absolute value of steering wheel angle by 0.27 degrees, the number of the road edge excursions by more than 8 cases, and the number of off-road crashes by almost 7 cases. These correspond to 30%, 30%, and 37% decreases in these outcome measures, respectively. These performance-based metrics have been associated with sleepiness-related road crash (either in simulator or on-road), and changes of these magnitudes may represent significantly reduced crash risk. These data together partly support the second hypothesis of an alerting effect of caffeine as opposed to the Placebo condition.

The combination of light and caffeine did not change any EEG-related outcomes. However, this condition had differential effects on ECG-derived outcomes. The mean beat-to-beat interval (mean RR) rose by 52 milliseconds (4 beats/min drop). These changes represent a change of 5%, a large effect of the intervention on these variables. Since the increase in mean RR (Borghini et al., 2014) or decrease in mean HR (Borghini et al., 2014; Liang et al., 2007) imply increased sleepiness, these findings suggest that the combination of light and caffeine could not improve these outcomes. Instead, these two outcomes degraded due to increased sleepiness.

The combination of light and caffeine seemed to improve the PPVT outcomes, increasing the percentage of correct responses and decreasing the percentage of lapses by about 7%. These changes suggest a medium effect of the intervention and significant improvement in reaction times under the combination of light and caffeine as opposed to the Placebo condition.

The combination of light and caffeine had a large effect on subjective sleepiness score by improving the KSS scores by 1.5 points from KSS value 6 ('some signs of sleepiness') in the Placebo condition to a value of 4 ('rather alert') after the intervention. This intervention could make sleepy drivers feel rather alert. One implication is that the administering light and caffeine in combination would give a sense of security to drivers regarding their sleepiness, and that they would continue driving in that context.

Of the driving performance outcome measures, there was a large effect of the combination of light and caffeine on the absolute value of lateral acceleration and the absolute value of the steering wheel angle with substantial decreases of 0.07 m/s^2 and 0.42 degrees (33%), respectively. These changes imply that drivers decreased the frequency of their abrupt lateral deviations and magnitude of their steering wheel movements. There were also eight (33%) fewer occurrences of road edge excursions with the combination of light and caffeine when compared with the Placebo condition. These findings indicate a significant improvement in driver performance.

Overall, the combination of light and caffeine did not significantly improve EEG and ECG-based outcomes of sleepiness, but did provide potentially considerable improvements in subjective alertness, PPVT, and driving performance outcomes of sleepiness. Therefore, the third hypothesis predicting the alerting effect of light and caffeine in combination is partly supported.

It is obvious that these three interventions do not exert their alerting effects on all levels of driver's sleepiness. There were no improvements in EEG or ECG-related outcome measures but some PPVT and driving performance benefits. It is unlikely that the unchanged EEG-based outcomes are due to poor sensitivity of EEG to sleepiness. There might be a mismatch between broader cortical EEG (including the specific recording positions) and the sensory-motor cortex functions associated with driving. Additionally, EEG and ECG-based outcome measures were each averaged over 30 min driving time. This averaging might have masked instantaneous changes of these variables at critical time points of driving. Therefore, there might be a need to analyse these data using different time bases (e.g. the point of roadway excursions/collisions, rather than overall).

The comparison of these three intervention types also revealed that they affect outcome measures in different ways. For example, EEG-derived outcomes of mean RR and mean HR did not change in response to light alone but were impaired with both caffeine alone and light and caffeine in combination. Conversely, PPVT outcomes measures did not change with light alone but improved with both caffeine alone and light and caffeine in combination. This implies that caffeine might exert its alerting effects on different pathways of alertness when compared with light alone.

The comparison of relative effectiveness of the three intervention types revealed no significant differences in EEG and ECG-based indices across these interventions. Having a small effect of receiving light and caffeine in combination, the percentage of lapses was 5.6% less, and the percentage of correct responses was 6% more than those with light only. However, light and caffeine in combination did not improve these metrics to a greater extent than did caffeine alone. Additionally, data showed a small effect of type of intervention on subjective sleepiness with lower sleepiness levels after light and caffeine in combination than after either light alone or caffeine alone. Data from the driving performance outcomes showed that with a medium effect of type of intervention, after light and caffeine in combination the absolute value of steering wheel angle was 0.3 degree greater than that of caffeine alone. The intervention type had a small effect on the number of road edge excursions, with the road edge excursions after light and caffeine in combination occurring more often than those observed after caffeine alone. These results show a greater alerting effect of caffeine than the light and caffeine in combination on the latter two variables. Overall, data partly supported hypothesis 4, predicting the advantage of light and caffeine in combination over the other two interventions.

The findings for the objective, subjective and driving performance outcomes did not support hypothesis 5, the prediction of a higher alerting effect of light relative to caffeine.

In spite of decreasing subjective sleepiness and improving the majority of driving performance outcome measures there was some deterioration in ECG-based outcome measures such as mean RR and Mean HR after administering an intervention (small to medium effects). These data partly supported hypothesis 6 that predicted a greater alerting effect of making an intervention when compared with the Placebo condition.

One important finding of the experimental study was the mismatch between subjective and objective sleepiness under all the three interventional conditions. The reasons for this discrepancy need to be studied further under another research paradigm. One reason for this discrepancy could be that it is not easy to have insight into the human physiological performance, to recognise cues of sleepiness associated with performance decline, nor to calibrate performance against subjective experience. The correspondence of each level of subjective sleepiness with drivers' objective performance is not well understood. The data from the current experimental study show that there were no strong associations between subjective sleepiness, PPVT performance and driving performance on the simulator. The potential discrepancy between subjective sleepiness and objective sleepiness may need to be taken into account when developing advertisements or similar road safety strategies against driver sleepiness. In advertisements it may be crucial to tell people not to rely on their own perception of sleepiness because subjective sleepiness may not reflect their real level of deteriorated performance. Instead, it could be reinforced that if drivers are not getting enough sleep (normally less than 8 hours), it will be more dangerous to drive. Literature suggests young drivers do not stop driving when they feel sleepy. This group of drivers may often have to drive while sleepy (when they stay up late or wake up earlier) for work, or because they have chosen to sacrifice sleep for socialization. Therefore, telling them not to drive when not having had enough sleep may not be effective. Advertisement or education-based methods have not yet been shown to be effective and should be developed and evaluated. This misalignment also has implications for current road safety strategies and justifies the need for prioritising the problem of sleepy driving, perhaps increasing the use of rumble strips, road side rest stops, and sleepiness-warning technologies inside vehicles. Using Actigraphy to give the drivers some feedback of their general level of sleepiness might be worth considering as a possible road safety strategy.

Findings of both the systematic review and the experimental study have some implications for our understanding of the mainstream bio-mathematical models of sleep-wake regulation, the neuroscience of sleepiness, and the neurocognitive substrates of driving. The systematic review showed some inconsistencies in the responses from different sleepiness outcome measures to sleep loss at different times of day. The current experimental study revealed that all of objective sleepiness and

driving performance outcomes, examined at 10 a.m. with low circadian sleepiness, do not respond to the three interventional conditions consistently. With regards to the bio-mathematical models, a very recent study reported that human cognition, including alertness and reaction time (which are particularly important for driving), are differentially sensitive to different processes of human sleep-wake regulation with inhibitory control being sensitive to the circadian processes and selective visual attention being modulated by sleep inertia (Burke, Tina M, Scheer, Ronda, Czeisler, & Wright, 2015). Therefore, it is highly likely for measures such as PPVT or driving performance to either remain unchanged or to degrade to different extents due to sleep loss alone (if primarily driven by the homeostatic drive for sleepiness) and hence, to differentially improve after light or caffeine in the current experimental study. Therefore, it may be crucial to run forced de-synchrony studies in driving paradigms to examine the sensitivity of a broad range of objective, subjective and driving performance outcome measures of sleepiness due to different circadian/homeostatic balance. The differentiated responses of outcomes to sleep loss and light/caffeine could be related to the neuroscience of sleepiness, and in fact be consistent with the involvement of different brain areas and pathways that subserve the different tasks involved during driving (Inc. reaction time, decision making, hazard perception and attitude). These skills might have different sensitivity to different types of sleepiness. The fact that no PPVT and driving performance outcomes failed after light/caffeine confirms the different sensitivity of these outcomes to sleep loss (homeostatic drive for sleep). There were strong changes in some outcomes showing their greater sensitivity to sleep loss and greater improvement after light/caffeine intervention. Changes of this magnitude are important in road safety because they could result in lower crash rates. It should be noted that there are other factors such as peer pressure, pressure of work, and increased distraction that could be included in the sleep deprived driving paradigm which would produce different outcome responses.

Different driving skills are balanced to meet the demands of various driving environments. For example, the predominant skills required for driving on a long rural highway (e.g. vigilance and control) might vary from those required in complex urban traffic (e.g. hazard perception). In the current experimental study, the driving scenario was a combination of straight highway, urbanised residential areas, and

curved sections. However, the specific responses of outcome measures were not analysed for each section. The specific sensitivity of outcome measures to sleep loss and light/caffeine interventions across a variety of driving contexts need to be examined.

There are some considerations associated with implementation of the Re-Timer and caffeinated chewing gum technologies into on-road mitigation strategies. Caffeinated gums were initially developed in a military environment and are now commercially available. There is no evidence available on the potential harm of these gums or their potential effectiveness on crash rates. Caffeine is currently habitually consumed by many drivers. It is not often regarded as a health intervention, and there are currently no government-driven rules or standardised timings and dosages of its consumption as a mitigation strategy for drivers' sleepiness. Given that some people cannot tolerate caffeine and some simply do not like its taste, it is also not known whether promoting caffeine as a countermeasure for drivers' sleepiness is an effective public health strategy. Therefore, the usability of caffeinated chewing gums needs to be examined.

The exposure to light might exert some minor side effects in some people such as discomfort, minor eye strain and a slight glare/headache. Some people might feel "weird" or stimulated exposure to light. It should be noted that risks associated with light are mostly attributed to light therapy methods in which bright light in high illuminances of more than 2500 lux is used for long times to treat people with depression (Terman & Terman, 1999). In this experiment the Re-Timer glasses, with small diodes in their frames, were adopted to produce a blue-green light with illuminance of 560 lux. This device was used in the study for 120 min by each participant (four times of 30 min). None of the above-mentioned side effects were reported by the participants. It should also be emphasised that if wearing the glasses degraded the drivers' performance in some way, their performance was still better than under the Placebo condition. It remains necessary to test a range of potential side effects of these glasses, and to test alternative sources of light, either mounted inside the dashboard (Okamoto et al., 2014) or provided in road side rest stops (e.g. via some form of light box). Blue-green light has the potential to interfere with the

colour perception of drivers, particularly during night time drives. Finally, their shape, design or price may have some hinder their usability in the real world.

Given the above-mentioned considerations, a complimentary study has been developed (HREC approval number: 1500000298) to examine the usability of the Re-Timer glasses and their feasibility as a countermeasure for drivers' sleepiness.

7.3 COMPARISON OF THE FINDINGS WITH THE LITERATURE

In this study monochromatic blue-green light (500 nm dominant wavelengths, illuminance 506 Lux, irradiance 230µW/cm^2, duration 30 min) and low dose of caffeine (100 mg) were administered.

The findings of this study are difficult to compare directly to the available evidence due to major differences in methodologies, time of day, outcomes, sleep deprivation and the characteristics of the light or caffeine (described in the systematic review Chapter 3:). Therefore, only the *directions of changes* in outcomes have been compared to those described in previous studies.

No differences in the EEG-based outcomes were observed while receiving the light alone or caffeine alone, except for a decrease in the variability of alpha EEG power after caffeine consumption. This single index could be an indicator of improved alertness conferred by the caffeine alone but not the light alone. Contrary to the findings from night time studies showing decreased alpha and theta EEG activity in response to the provision of *light* (An et al., 2009; Cajochen, Christian et al., 2000; Figueiro, M.G et al., 2009; Phipps-Nelson et al., 2009), findings from previous daytime studies are mostly consistent with the results of this study. For instance, Badia et al. (1991) did not find any significant difference in the log power density of alpha and theta EEG bands during daytime exposure to high levels of bright white light. An et al. (2009) found that exposure to either blue or red light during the daytime did not attenuate alpha EEG power significantly. Some other daylight studies, however, have shown some changes in EEG activity. Okamoto et al. (2014) reported that during the daytime EEG alpha power was lower under blue light, as opposed to darkness. There may be methodological reasons for the inconsistency between the current findings and those reported by Okamoto et al. (2014). In their

study participants were partially sleep deprived during one night, for 1.5 hours in the early morning, while in the current study participants experienced half of that sleep restriction (45 minutes).

In the current study there were significant increases in mean cardiac beat-to-beat interval (mean RR), and reciprocal decreases in mean heart rate (mean HR) in response to both caffeine alone, and light and caffeine in combination. Since mean RR typically increases during the transition from wake to sleep during the sleep onset period (Boudreau et al., 2013; Trinder, John et al., 2001), the increase in this variable could be attributed to increased sleepiness after these two interventions. The changes in these two autonomic indices could also be the result of caffeine withdrawal before the experiment.

In this experimental study mean RR and mean HR both remained unchanged under light alone. It can be implied that although the light could not improve sleepiness, it could at least potentially prevent the progression of sleepiness.

Rüger et al. (2006), also did not find any changes in heart rate after 4 h exposure to 5000 lux bright light during the daytime, while they reported an increase in heart rate after exposure to night time light in the same level and duration. In another daytime study, there was no significant differences in ECG-derived indices such as mean HR, percentage of successive RR intervals differing more than 50 milliseconds, LF HRV, HF HRV and LF/HF HRV between the Placebo condition and either 100 mg caffeine or 200 mg caffeine conditions (Rauh, Burkert, Siepmann, & Mueck-Weymann, 2006). Figueiro et al. (2009) found an increased mean RR after night time exposure to 40 lux of blue light. Since the circadian drive for sleep is known to increase mean HR (Boudreau et al., 2013; Trinder, John et al., 2001), the aggravating of ECG-derived sleepiness outcomes during night time but not daytime, could be attributed to the contribution of the circadian drive to sleepiness at night.

Regarding PVT performance, the findings of the current study revealed that the combination of light and caffeine decreased the percentage of lapses and increased the percentage of correct responses as opposed to the Placebo condition. Light however, did not result in any change any of these outcomes when compared with the Placebo condition. Even though caffeine significantly improved these two variables relative to the Placebo condition, there were no significant differences in

the values of these two variables after receiving caffeine alone when compared to light alone (no change across these two intervention types).

The studies reviewed previously (Chapter 4:) confirm these findings by reporting either ineffectiveness of light or no special advantage of caffeine over light. For instance, Phipps-Nelson et al. (2009) found no main effect for light on percentage of PVT lapses. They even reported an increased percentage of lapses during their night time study, probably due to an increased circadian sleepiness component. Hartley et al. (2013) did find an immediate effect after the 30 min administration of night time light or caffeine, but did find a delayed response 5 h after these interventions, with fewer lapses after caffeine than after the Placebo condition or after light alone. When compared with 100 mg caffeine in the current study, the high dose of caffeine (capsules of 200 mg) in the Hartley et al. (2013)study might have exerted a greater alerting effect. Additionally, the follow-up measurement of these outcomes after 5 h revealed some improvements which were not observed immediately. However, it should be noted here that a 5 h delay in improved alertness is not consistent with the intent to use caffeine as an acute alerting agent to combat sleepiness while driving.

Significant improvements in subjective sleepiness were observed after all three conditions when compared with the Placebo condition, with light and caffeine in combination having greater improving effect than either light alone or caffeine alone. The effect of light alone was equivalent to that of caffeine alone. This finding is comparable to those of some previous studies. Hartley et al. (2013) found that caffeine was more effective than light in improving sleepiness ratings. As before, one explanation for the higher effectiveness of caffeine for subjective sleepiness could be the higher dose of caffeine (200 mg) provided by Hartley et al. (2013) than was provided in the current study. Two other studies by Cajochen et al. (2000) and Ruger et al. (2006) also support these results, with the former reporting a rapid improvement in subjective sleepiness after bright light (9100 lux) provided at night compared with l00 lux and 3 lux lights, and the latter reporting an equal improvement in subjective sleepiness after bright light (5000 lux) in both the daytime and at night. The high levels of light used in the study of Cajochen et al. (2000), and long-time exposure to the light (4 h) in the study of Ruger et al. (2006) provided a greater photon ‘dose’ than in the current study. Conversely, some studies did not find

any changes in subjective sleepiness after exposure to light. In a study by Figueiro et al. (2009), an alternative exposure to 45 min of blue light (40 lux and 10 lux) and 45 min darkness during the night resulted in neither increase nor decrease in the subjective sleepiness. Other studies recorded subjective sleepiness for longer periods across the night time hours and reported that sleepiness either degraded across the night after exposure to blue light (1.12-1.15 lux for 6 h) (Phipps-Nelson et al., 2009), or remained unchanged up to 1 h after 6.5 h exposure to blue light (12.1 $\mu W/cm^2$) and then degraded (Lockley et al., 2006). This could be due to the progressive predominance of the circadian pressure for sleep during night time hours, especially across the circadian temperature nadir.

Of the driving performance outcomes, the steering wheel angle was found to be the index most sensitive to the light and the caffeine interventions used in the current study. All interventions of the combination of light and caffeine, caffeine alone, and light alone, resulted in significantly decreased steering wheel angle compared to the Placebo condition, with the combination of light and caffeine having a considerably greater effect than light alone. This finding is consistent with the findings of Forsman et al. (2013). They examined more than 80 objective driving performance outcomes among sleep-deprived drivers. After principal component analysis they concluded that of all these driving performance outcomes, two dominant groups of variables, *steering wheel variability* and *lateral lane position variability*, were the most sensitive to driver sleepiness. Further, these two indices were, more than any other outcome measure, directly predictive of line crossings, off-road accidents, and hitting adjacent cars.

In the current study, the total number of road edge excursions reduced after receiving caffeine alone and to a greater extent after light and caffeine in combination when compared to the Placebo condition. The total number of off-road crash (when the centre of the car crossed the road edge line by 0.99 m) reduced after administering caffeine alone. The total number of speed exceedances only reduced after receiving light alone. Additionally, unlike the findings of Forsman et al. (2013), no overall effect of the "Intervention" was observed on the standard deviation of lateral position (i.e. lane position on the simulated roadway).

Findings of Taillard et al. (2012) and Hartley et al. (2013) are partly consistent with these results. In the study conducted by Taillard et al. (2012), the road edge excursion (inappropriate line crossing) decreased with both blue light (7.4 μw/cm^2) and caffeine (2*200 mg) as opposed to the Placebo condition. The decrease in the number of road edge excursions by light alone in their study could be attributed to the long exposure time (4 h) to blue light. Hartley et al. (2013) observed an overall effect of the intervention (bright light alone 10000 lux, caffeine 200 mg, or combination of them) on off-road crash (when the centre of the car crossed the edge of the lane). The latter authors also found a smaller speed deviation (as the mean sum of differences between speed of the vehicle and speed limit) with light alone (10000 lux) than the Placebo condition in the first 2 h (at 3 a.m.).

The ineffectiveness of the light in this experimental study is in line with the findings of some other studies. For instance, Phipps-Nelson (2009) did not find any overall effect of the 'Intervention" on the standard deviation of lateral lane position. This variable worsened over the night with blue light (2000 μW/cm^2). However, Taillard et al. (2012) found an overall effect of the "Intervention" on this variable. They reported that both blue light (7.4μW/cm^2) and caffeine (2*200 mg) decreased the mean standard deviation of lateral lane position as opposed to the Placebo condition. Hartley et al. (2013) also found some delayed decreases in the standard deviation of lateral position 2 h post-administration of the light and caffeine in combination when compared with the Placebo condition.

One reason for not observing the change in the standard deviation of lateral lane position in the current study was the fact that in the driving scenario a four-lane highway was simulated with two ongoing lanes on the left side. Since all ongoing cars were moving in the adjacent lane, there was no need to overtake any car (Section 5.3.2; the STISIM Drive simulator). The other reason for not finding any changes in this variable is that unlike the Hartley et al. (2013) study, in this experimental study the driving performance data were only measured when the light was administered. There may have been some alerting effects of the interventions at some point after administration. Additionally, administering higher doses of caffeine (Hartley et al. (2013); 200 mg and Taillard et al. (2012); 400 mg) and the presence of higher levels of sleep restriction at night in these two studies (4-6 hours) might have

resulted in the significant improvement in the standard deviation of lateral lane position**.** An important point to note is the role of the circadian rhythm of sleepiness resulting in different levels of sleepiness at different times of day (Phillips, 2015). Timing of exposure to light and caffeine changes the phase of circadian rhythm. In one study examining the response of the circadian rhythm to 3 h exposure to 9000 lux full-spectrum light it was observed that the circadian rhythm was relatively unresponsive to light when exposure was centred 6 h after minimum core body temperature (light exposure happened around 10-11 a.m.), but there was a large phase-delay in circadian rhythm when the light was centred 2 h before body temperature minimum (Minors, Waterhouse, & Wirz-Justice, 1991). Caffeine has also been found to phase shift human circadian rhythm. In one study administering 2.9 mg/kg caffeine 3 h before habitual bedtime resulted in 1 h phase delay in circadian rhythm (Burke, Tina M., 2011). These findings imply that the timing of administering the three types of intervention (light, caffeine and light and caffeine combination) might have different effects on circadian rhythm and hence the level of sleepiness. In this experimental study the implications of the circadian drive on sleepiness were considered. The test time was set at the peak time of alertness in the day around 10 a.m. A very recent report (Wright, K. P. et al., 2015) suggests a strongly differential sensitivity of specific aspects of sleepiness (and associated measures) under variation in circadian and homeostatic loads.

Another point is that caffeine curfew and withdrawal prior to testing (an aspect of the study methodology) might impact the driver's performance before the administration of the light/caffeine. Even though no withdrawal effects of caffeine have been reported in some studies (Bonnet, Michael H & Arand, 1992), in some cases an overnight caffeine withdrawal resulted in greater sleepiness, deteriorated mental alertness, and increased simple and choice reaction times in the afternoon. Administering 250 mg caffeine improved these measures in consumers of more than 40 mg/day (medium-high consumers) but did not affect measures in non-consumers of caffeine (Rogers, Peter J., Heatherley, Mullings, & Smith, 2013). This raises the possibility that the observed alerting effects of caffeine could be partly due to a withdrawal effect. In other words, deterioration of sleepiness indicators, such as driving performance and PVT outcomes, prior and during the first drive might be due to caffeine withdrawal (after a 9-h caffeine curfew) rather than due to sleepiness. As

a result, the improvements in sleepiness outcomes during and after the second drive might be because of caffeine withdrawal reversal (the consumption of caffeine in the form of the Active gum) and the differential impacts associated with individual variation in use, metabolism and tolerance of caffeine, and not because of a more specific alerting effect of caffeine. Comparisons of findings for the objective, subjective sleepiness and driving performance outcome measures in the current study with the literature are presented in Table 6.12 and Table 6.13 respectively.

Table 6.12 Comparison of findings the objective/ subjective sleepiness outcome measures in the current study with the literature

Outcome measure	EEG Alpha power	SD of EEG alpha power	EEG Theta power	SD of EEG theta power	Mean RR (millisecond)	SD of RR (millisecond)	Mean HR (beats/min)	SD of HR (beats/min)	LF	HF	LF/HF	KSS
Current study	No main effect of intervention/ intervention type	0.962 decrease (28%) by caffeine, No main effect of intervention type	No main effect of intervention/ intervention type	No main effect of intervention/ intervention type	Increased by 5% and 10% under caffeine and the combination. No main effect of intervention type	No main effect of intervention/ intervention type	Decreased by 5% under both caffeine and the combination. No main effect of intervention type	No main effect of intervention/ intervention type	No main effect of intervention/ intervention type	No main effect of intervention/ intervention type	No main effect of intervention/ intervention type	0.9, 0.966 and 1.533 score decrease by light, caffeine and combination, 2-1 = 0.650, 3-1 = 0.58
Figueiro et al. 2009	Decrease in the EEG alpha power by 10 and 4 lux blue light				Increased by 40 lux of blue light							No main effect of intervention/ intervention type
Cajochen et al. 2000	Decreased by 100 and 9100 lux		Decreased by 100 and 9100 lux									Rapid improve under 9100 lux, dependenc

Outcome measure	EEG Alpha power	SD of EEG alpha power	EEG Theta power	SD of EEG theta power	Mean RR (millisecond)	SD of RR (millisecond)	Mean HR (beats/min)	SD of HR (beats/min)	LF	HF	LF/HF	KSS
												y of KSS to light level
Phipps-Nelson 2009	No main effect of intervention/ intervention type		Decreased by blue light									No main effect of intervention/ intervention type. Increased across the night
Okamoto 2014	Lower under blue and red light than dim light		Increased after 60 minute after test									
Badia et al. 1991	Not changed		Increasing the EEG theta power across night, but not day									

Outcome measure	EEG Alpha power	SD of EEG alpha power	EEG Theta power	SD of EEG theta power	Mean RR (millisecond)	SD of RR (millisecond)	Mean HR (beats/min)	SD of HR (beats/min)	LF	HF	LF/HF	KSS
Ruger et al. 2006							Increased by night time light, not daytime					Similar improving effect of light on KSS on day and night
An et al. 2009	Higher alpha attenuation in night time than day											Not changed, both night and day
Lockley et al. 2006	Increased by blue light		Decreased by blue light									No effect of light condition up to one hour after light, increased sleepiness after that time

Outcome measure	EEG Alpha power	SD of EEG alpha power	EEG Theta power	SD of EEG theta power	Mean RR (millisecond)	SD of RR (millisecond)	Mean HR (beats/min)	SD of HR (beats/min)	LF	HF	LF/HF	KSS
Lafrance et al. 1998												Increased KSS after 2 nights sleep loss, no improvement by day time bright light,
Hartley et al. 2013												(VAS scores) worsened under the Placebo condition throughout the night with the highest sleepiness at 6 a.m. VAS sleepiness score was improved at 6 am

Outcome measure	EEG Alpha power	SD of EEG alpha power	EEG Theta power	SD of EEG theta power	Mean RR (millisecond)	SD of RR (millisecond)	Mean HR (beats/min)	SD of HR (beats/min)	LF	HF	LF/HF	KSS
												with a more effect of caffeine than light.

1 = combination of light and caffeine, 2 = light, 3 = caffeine

VAS: Visual Analogue score, KSS: Karolinska Sleepiness Score,

SD = Standard deviation

Table 6.13 Comparison of findings for driving performance outcome measures in the current study with the literature

Outcome measure	Percentage of lapses	Percentage of correct responses	Mean slowest 10% of 1/RT	Mean reciprocals of correct and lapses	Steering wheel angle	SD of lateral lane position	Total number of collisions	Total number of road edge excursions	Total number of off-road crash	Number of speed exceedances
Current study	6.17% and 7% increase by caffeine and combination, 1-2 = 6.015	6.25% and 7% decrease by caffeine and combination,	Caffeine caused a 0.12/s increase (5%), 1-2 = 0.206	No main effect of intervention, 1-2 = 0.206	0.22 degree (22%), 0.27 degree (30%), 0.42 degree (33%)decrease by light, caffeine and combination, 1-3 = 0.297	No main effect of intervention/ intervention type	No main effect of intervention/ intervention type	8.2 cases (30%) and 8.3 cases (33%) decrease by caffeine and combination, 1-3 = 6.367	6.8 crashes (37%) decrease by caffeine, No main effect of intervention type	2.5 cases (19%) decrease by light, 1-2 = -2.383, 2-3 = 2.217
Figueiro et al. 2009		No effect on simple RTs type								
Phipps-Nelson, 2009	No main effect of intervention/ intervention type, Increased across the night	Mean RTs decreased under blue light than dim light				No main effect of light condition, worsened under all light conditions				

Outcome measure	Percentage of lapses	Percentage of correct responses	Mean slowest 10% of 1/RT	Mean reciprocals of correct and lapses	Steering wheel angle	SD of lateral lane position	Total number of collisions	Total number of road edge excursions	Total number of off-road crash	Number of speed exceedances
Lockley et al. 2006	Decreased by blue light	Decreased under blue light more than red light								
Lafrance et al. 1998	Increased over days of light exposure	Decreases across 2 days of light exposure								
Taillard et al. 2012						Decreased by both blue light and caffeine than Placebo		Decreased by both blue light and caffeine than Placebo		
Hartley et al. 2013	A main effect of intervention on the number of lapses at 6 a.m., with caffeine decreasing the number of lapses			Global effect of intervention on mean RRTs with the highest effect at 6 a.m., More improvement in mean reciprocals of reaction times		Main effect of intervention. Lane drifting decreased by combination of light and caffeine compared to the Placebo		Main effect of intervention. Number of crash decreased by intervention, with the highest effect at 6 a.m.		

Outcome measure	Percentage of lapses	Percentage of correct responses	Mean slowest 10% of 1/RT	Mean reciprocals of correct and lapses	Steering wheel angle	SD of lateral lane position	Total number of collisions	Total number of road edge excursions	Total number of off-road crash	Number of speed exceedances
	more than light			after combination of light and caffeine than either of the Placebo condition (p = 0.018) or light alone (p = 0.029), and after caffeine alone when compared with light alone (p = 0.029).		condition 2 h				

1 = combination of light and caffeine, 2 = light, 3 = caffeine

7.4 CONTRIBUTION OF THIS PROGRAM OF RESEARCH TO THE EXISTING KNOWLEDGE

The current program of research has added some novel findings to existing knowledge as follows:

1. As part of this program a systematic review was conducted for the first time on the effects of sleepiness on young driver's performance. The systematic review revealed the paucity of this information with a very limited number of available papers on this subject (only 10 papers). Studies of chronic sleep loss on daytime sleepiness of young drivers are particularly rare.
2. For the first time some important methodological characteristics of papers on young drivers' sleepiness were identified that could degrade or upgrade the quality of papers for certain outcome measures. These characteristics fit in some broader classes of the GRADE criteria such as risk of bias and imprecision.
3. This program introduced a novel approach in the field of road safety for rating the quality of papers for their outcome measures by developing specific GRADE rating criteria for drivers' sleepiness. In this method papers with a medium quality for one outcome measure might be identified as a low-quality paper for another outcome measure and vice versa.
4. Considering the sample sizes, for the first time in the field of road safety, a new algorithm was introduced to identify the overall GRADE Score (OGS) for the quality of the whole body of evidence for a certain outcome measure.
5. For the first time different ranges of Overall GRADE Scores were assigned to different GRADE quality levels from very low quality level to high quality level.
6. The existing knowledge about the alerting effects of light and caffeine on sleep-deprived drivers mostly stems from two relevant studies (Hartley et al., 2013; Taillard et al., 2012). Both these studies were undertaken at night after a single night of sleep deprivation, provided high doses of caffeine or long exposure to light, and examined limited outcomes. Additionally, Hartley et al. (2013) assessed the effects of white light rather than blue light. This current

experimental study was the first to take into account the high sensitivity of young drivers to sleep loss and subsequently targeted only young drivers.

7. This program benefitted from an innovative experimental study in that it addressed the need for a chronic restriction paradigm to better reflect young adult sleep deprivation. The type of sleepiness induced in this study was a chronic mild sleep deprivation (1 h) which young drivers frequently suffer from and had not been previously studied. Additionally, early morning wake-up was chosen to induce sleepiness, since this type of sleep deprivation deteriorates sleepiness outcomes to a greater extent than does wakefulness extended into the evening (Darwent et al., 2010). The sleep deprivation was a naturalistic home-based sleep loss mapped onto the drivers' real sleep paradigm although this form of sleep loss causes some noise on the effect and makes it harder to control some contributors to sleepiness.
8. The experimental study took a multi-model design by comparing the effects of the three interventional conditions on different outcomes of sleepiness in all objective, subjective, and driving performance levels. The existence of misalignment between subjective and objective sleepiness outcome measures confirmed the need to measure all levels of sleepiness and not be restricted to limited numbers of driving performance outcome measures.
9. This study was conducted during the daytime, and at the same time each day. This aspect limited the variation in the circadian drive for sleepiness, while previous studies have not distinguished the homeostatic drive from the circadian drive.
10. In this study a constant level of blue light and a low dose of caffeinated chewing gum were administered for the first time in a driving paradigm to evaluate the alerting effects of commercially available light and caffeine technologies. This makes it feasible to test these technologies in the real world. These two forms of light and caffeine have not been used together before.
11. The driving performance measures were specific to the three newly developed driving scenarios presented by the STISIM Drive simulator. The

majority of the driving outcomes have not been studied in chronically sleep deprived young drivers before, such as the absolute value of lateral acceleration, LF, HF and LF/HF components of heart rate variability, the absolute value of steering wheel angle and the total number of off-road crashes. This approach provided an opportunity to observe some novel results - for example, the absolute value of steering wheel angle was the most sensitive outcome measure to manipulations of light and caffeine and significantly improved with all the three types of intervention.

7.5 CONSIDERATIONS

There are some considerations to be taken into account when interpreting the outcomes of this experimental study, associated with both the recruitment process and the conducting of the testing.

Assessment of participant age, health status, taking medicines or illicit drugs, habitual consumption of alcohol or caffeine and driving experience (holding a valid driver's licence) was based on self-reported data, largely due to ethical considerations. There might have been some deviations from the inclusion criteria. However, the within-participant study design was highly likely to eliminate the effect of inter-individual differences.

Even though participants were instructed to refrain from consumption of alcohol totally and adhere to a 9 h caffeine curfew during the last three days, there was no monitoring tool, such as blood testing, to strictly control for alcohol or caffeine use. This might have affected the sleepiness levels caused by partial sleep deprivation.

The current study was conducted on the driving simulator not on real roads due to technical difficulties in collecting EEG data during on-road driving, and the need to provide a controlled light environment during the daytime. Driving simulators have been criticized for inducing fatigue more quickly than observed during on-road experiments (Philip et al., $2005_{(b)}$). Therefore, there is a need for further on-road research (with relevant contextual or motivational stimuli underlying this effect) to verify the effect of this level of blue light and this dose of caffeine in the real world.

It possible that light emitted from the STISIM Drive display screen masked some alerting effects of the blue-green light. To minimise the interference of light emitted by the simulator screen, all computer displays were covered by neutral density grey filters. These filters reduce the brightness of light emitted from display screens without affecting objects' colours in the graphics shown by the simulator.

Given the difference in pupil diameter and its response to the light among people (Feigl et al., 2012), the actual light levels received by retina might have been different across participants in this study. This aspect is rarely controlled for in sleep circadian studies (Zele et al., 2011).

In this study the distance between the simulator screen and participants' eyes varied between the participants due to the immobile steering wheel of the simulator. In fact, participants had to adjust their distance from the screen by moving the chair back and forth to be able to control the steering wheel properly. This variation might have affected their visual input. The within-participant design was intended to mitigate this difference.

In the current study the measurements of objective and driving performance outcomes of sleepiness were conducted concurrently with the administration of the light, while other measures were made immediately after 30 min exposure to the light. This granularity in the timing of measurement might not have captured some possible alerting effects.

The duration of simulated driving time in the current study was limited to 30 min for two reasons; firstly, caffeine seems to reach its minimum level in the blood in an average 30 min (Blanchard & Sawers, 1983; O'connell & Zurzola, 1984). Secondly, time-on-task effect or fatigue from driving is highly likely to emerge after 30 min driving (Van der Hulst et al., 2001). It remains quite possible that a longer driving time could reveal greater alerting effects of light and caffeine.

The presentation of the Placebo condition first could have had a systematic effect on the results, such as a false positive impact from the interventions in the case of presence of any practice effect on the driving task. The practice effect could result in false improvements in driving performance and PVT outcomes. To minimize learning effects, three different scenarios with identical road sections but different

road sceneries were counterbalanced across the three test days. Additionally, within each test day, and in order to minimize the learning effect between the first drive and second drive on the same scenario, a random selection of immobile and mobile cars, pedestrians and buildings was included in the scenario. Therefore, the drivers would not be able to remember the exact sequence of events in the second play of the same scenario. The driving task did not include any predictable events such as the sudden appearance of objects, cars, or pedestrians in the scenario. As for the PVT, the red dot appeared in the intervals of 2 to 12 seconds and drivers could not anticipate the time of appearance of the red dot. There is no strong evidence of learning effects on the PVT including use of this test in very similar paradigms (Cluydts et al., 2002; Jackson et al., 2013; Lim & Dinges, 2008; Ting et al., 2008; Van Dongen & Dinges, 2005). The three conditions were also counterbalanced across three days so any possible learning effect would be distributed across the conditions."

With regards to effect of light, one might expect that withdrawal effect of light (adaptation to darkness) might also have increased sleepiness and have deteriorated performance prior to testing by interrupting the natural process of exposure to light and modulation of circadian alerting effect of light. There is no evidence that low levels of dim red light makes drivers sleepy. Instead, it may 'unmask' incipient sleepiness. The relationships between prior light exposure and the effects of light are likely to be complex, but are currently unknown.

There are some new questions raised from this research that need to be answered by further research, as follows:

1. What are the *delayed* effects of light, caffeine or combination of light and caffeine on all levels of sleepiness after administering these countermeasures?
2. What are the effects of light, caffeine or combination of light and caffeine on all levels of sleepiness in *different times of day*?
3. What is the best intensity of blue light with the most alerting effect and least glaring effect?
4. What is the optimal wavelength of blue light with the greatest alerting effect and least interference with colours and contrast in the driving environment (including road signals, and the headlights of upcoming cars at night)?

5. What are the lasting (washout) periods for the alerting effects of light and caffeine or light and caffeine in combination?
6. Are the Re-timer glasses feasible for use in the real world?

7.6 LIMITATIONS

In this study no baseline measurement of outcomes without sleep loss was conducted. Therefore it was not possible to monitor the changes of outcomes after sleep loss compared to normal sleep. Additionally, based on the systematic review in this program of research, data and evidence on the values of different objective sleepiness and driving performance outcomes in normal conditions and after sleep loss, particularly after mild sleep loss, are not available to provide a robust conclusion on the alerting effects of the three conditions.

Chapter 8: Conclusion

An overall conclusion of this research is provided in Section 8.1. In Section 8.2 the remaining gaps in the knowledge are provided, followed by some future studies recommended in Section 8.3. Finally, some methodological pieces of advice are included in Section 8.4.

8.1 CONCLUSION OF THIS PROGRAM OF RESEARCH

The blue-green light and caffeine when administered alone or in combination have some alerting effects on various outcome measures of sleepiness. The data partly support the overall effect of the "Intervention" when compared with the Placebo condition. Therefore, the greater alerting effects of light alone, caffeine alone or the combination of them compared to the Placebo condition are partly supported. Data are also partly in agreement with the hypothesis of the greater alerting effect of light and caffeine in combination than either light alone or caffeine alone, but do not support the hypothesis that light alone has greater benefits than caffeine alone.

8.2 REMAINING GAPS IN THE KNOWLEDGE

This program of research provided some answers about the effectiveness of light and caffeine alone or combined together on daytime sleepiness from sleep loss (homeostatic sleep drive). However, there are still some major gaps remaining in the current knowledge, as follows.

1. The pathways for effects of sleep loss on driver sleepiness in objective, subjective and driving performance levels are not fully determined. Accordingly, the most sensitive outcome measures of driver's sleepiness are not identified.

2. The effects of homeostatic and circadian drives on young driver's sleepiness are not fully understood and distinguished.
3. The effectiveness of light and caffeine alone or combined together in relation to sleep homeostatic (different types and doses of sleep loss) and circadian factors (different times of day) is largely unknown.
4. This program of research did not intend to compute a new alertness model by including light and caffeine in the current sleep-wake regulation models. Therefore, fitting light and caffeine in current available models remains to be done.
5. This program of research adopted a pragmatic approach by using the available technologies (the Re-timers and caffeinated chewing gums) to provide constant light and caffeine doses. Therefore, optimal light properties (e.g. intensity, wavelength) or caffeine doses to exert the highest alerting effects are not still known. New light devices and/or caffeine modalities are likely to emerge, each with different properties.
6. Since in this experimental study a caffeine curfew was adopted for habitual caffeine users, it is not known whether the alerting effects of caffeine are due to stimulating properties of caffeine itself or from its paradoxical physiological effects from caffeine withdrawal.
7. The usability of the Re-timer glasses in the real world remains to be studied, particularly in terms of driver eye comfort and willingness of drivers to use them.
8. The interaction of light with the surrounding environment for driver safety, particularly for night time drives is not known.
9. Since there is no consensus on washout periods for light or caffeine in the driving context, the delayed effects of light, caffeine or combination of light and caffeine on all levels of sleepiness after administering these countermeasures is not well understood.
10. Light and caffeine exert their alerting effects on different levels of driver sleepiness. However, the pathways of those effects are not well understood.

11. The effects of combinations of light with other countermeasures such as naps or exercise on young drivers' chronic sleepiness indices are not known.
12. There is a lack of data on sleepy driving and alerting effects of light, caffeine or other countermeasures in on-road driving experiments.
13. Potential risks from light such as eye strain, headache, nausea and feeling 'wired' have been mostly observed in light therapy studies. In the current experimental study none of these effects were observed. However, there is no data available for these side effects in the sleepy driving studies.

8.3 RECOMMENDED FUTHER RESEARCH

1. High-quality evidence such as randomized control trials (RTCs), large-scale studies or strong experimental designs must be undertaken to provide reliable data for behaviour of sleepy young drivers, the pathways involved, and the most sensitive outcome measures of driver sleepiness.
2. The contribution of circadian and homeostatic drives to driver sleepiness should be taken into account in developing the RTCs and large scale studies by adopting different types and doses of sleep loss at different times of day. One possible approach is to include sleep deprivation and light/caffeine interventions into modified constant routine protocols to examine the effect of time of day on the alerting effects of the light and caffeine alone in sleepy drivers. This would involve adopting a sleep laboratory protocol to monitor the sleep-wake regimes precisely, at the cost of naturalistic evaluation.
3. Caffeine-based and light-based RCTs or large scale studies need to be conducted to provide high-quality evidence of the alerting effects of these stimulants on young driver chronic sleepiness.
4. The effects of caffeine withdrawal on driver sleepiness should be distinguished from the adverse effects of sleep loss.
5. Combination of light or caffeine with other countermeasures such as naps or exercise should be studied in the sleepy driving context and those findings must be verified in on-road experiments.

8.4 METHODOLOGICAL SUGGESTIONS FOR THE FUTURE STUDIES

Based on the methodology utilised in this experimental study the following considerations are suggested for future similar studies:

1. It is suggested that the baseline measurements without sleep deprivation are conducted to monitor the changes of outcomes after sleep loss compared to normal sleep. These measurements would permit comparisons of the alerting effects of counterbalanced conditions after sleep loss with baseline alertness without sleep loss.
2. Recording of objective outcome measures such as EEG and ECG-related outcomes could be more closely synchronized with the sampling by the driving simulator. This would facilitate instantaneous measurement around critical events such as crashes.
3. Follow-up measurements should be recorded for at least several hours after the interventions to track any delayed responses to alerting effects of light, caffeine or other countermeasures for sleepiness.
4. EEG and ECG-derived variables could be averaged across shorter time epochs to track short-term changes in those variables, particularly around critical events such as crashes, road edge excursions, line crossings and speed exceedances.
5. The illuminance and irradiance of the confounding light emitted from the simulator displays should be measured, even after using light filters, to determine the possible share of this light at the eye level or in the retina.
6. To retain a constant distance between participants' eyes and the desktop simulator screen (STISIM Drive) a potential approach would be to mount the simulator screen on an adjustable table with sliding parts to adjust the steering wheel and gas pedal distances and set a constant distance of simulator screen for all participants.
7. In case of using higher illuminances a diffuse light to avoid glare and discomfort should be provided.

8. In order to study the confounding effects of caffeine withdrawal on driver sleepiness, there is a need to conduct a pilot study without sleep deprivation. The drivers' sleepiness after caffeine withdrawal (without sleep loss) should be measured before caffeine treatment and compared with those values after caffeine treatment. Otherwise, a washout period of a minimum four days is suggested to eliminate any carryover effects and withdrawal effects of caffeine (Sondermeijer, van Marle, Kamen, & Krum, 2002).

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Appendices

Appendix A

Phone call screening questionnaire

Inclusion criteria

1. How old are you?
   Less than 18 years 18-24 years 25 years or more
2. Are you holding a driver's licence?
   Yes No
3. Do you have any physical restrictions to drive?
   Yes No

Exclusion Criteria

4. Are you a professional driver?
   Yes No
5. Have you been doing shift work during last month?
   Yes No
6. Have you travelled to different time zones in the last month?
   Yes No
7. Do you usually go to sleep after 12am (midnight)?
   Yes No
8. Do you have any acute illness particularly neurological diseases such as dementia, cardiovascular diseases, balance problem, or mental disease?
   Yes No
9. Do you have any eye or optic nerve diseases that affect your normal vision and are a problem for driving?
   Yes No
10. Do you usually drink more than 2 standard alcoholic drinks per day? (One standard drink contains 10 grams of alcohol)
    Yes No
11. Are you taking prescription medications such as melatonin, Antihistamines, Antidepressants, barbiturates, methaqualone and diazepam?
    Yes No
12. Are you taking illicit drugs s such as opium, heroin, cocaine, Marijuana, Hashish, amphetamine, amphetamine-type stimulants and ecstasy?
    Yes No
13. Are you a caffeine avoider (do not consume caffeine)?
    Yes No

14. Are you a heavy caffeine user (e.g. drink more than 3 caffeinated drinks per day)?

Yes No

Screening result

Is this prospective participant likely to be eligible for this study?

Yes No

Appendix B

Screening checklist

(All comments and responses will be treated confidentially)

Participant name:

Date:

Part A: Inclusion and exclusion criteria

Inclusion criteria

1. How old are you?
   Less than 18 years 18-24 years 25 years or more
2. Are you holding a driver's licence?
   Yes No
3. Do you have any physical restrictions to drive?
   Yes No

Exclusion Criteria

4. Are you a professional driver?
   Yes No
5. Have you been doing shift work during past month?
   Yes No
6. Have you travelled to different time zones in the last month?
   Yes No
7. If yes where did you go and when?

8. Do you have any of these diseases?
9. Neurological diseases such as dementia,

a. Cardiovascular diseases,
b. Balance problem,
c. Major mental disease
   Yes No

10. If yes which one?
11. Do you have any eye or optic nerve diseases that affect your normal vision and are a problem for driving?
    Yes No
12. If yes what is your eye problem?

13. Do you usually take more than 2 standard alcoholic drinks per day? (One standard drink contains 10 grams of alcohol)

Yes No

14. If yes what type of drink and how much per day?

15. Have you been taking one or more than one of these illicit drugs**?**

a. **Opiates (**Naturally extracted or semi synthetic drugs) such as opium, morphine, codeine and heroin

b. **Opioids** (wholly synthetic products) such as methadone, pethidine and fentanyl.

c. Sedative-hypnotics such as Methaqualone

d. **Stimulants** such as cocaine hydrochloride and crack cocaine, amphetamine and amphetamine-type stimulants (ATS), MDA (3,4-methylenedioxy-amphetamine) and MDMA (3,4-methylenedioxy-methamphetaime or ecstasy)

e. **Cannabis** such as Marijuana and Hashish

16. Have you been taking prescription medications?

- Beta blockers, melatonin, or melatonin agonists
- Psychoactive medications such as:
  - Cocaine
  - Antihistamines,
  - Antidepressants,
  - Anxiolytics, anticonvulsants such as barbiturates, non-barbiturate depressants (Methaqualone) and benzodiazepines (diazepam or Valium)

Yes No

17. Are you a caffeine avoider (do not consume caffeine)?

Yes No

18. Are you a heavy caffeine user (e.g. drink more than 3 caffeinated drinks per day)?

Yes No

Part B: Questionnaires scores

Questionnaire	Score	Exclusion criteria	Comments
Lifestyle Appraisal Questionnaire score		-	
Pittsburg sleep quality index		PSQI TOTAL > 5 (poor sleep quality) OR TMPHSE less than 85	
Epworth sleepiness scale		Score greater than 10 (excessive daytime sleepiness)	
Morningness- Eveningness Questionnaire		Scores between 16 to 30 (Extremely evening type)	

Screening result

Is this prospective participant eligible for this study?

Yes No

Appendix C

Lifestyle Appraisal Questionnaire (LAQ)

Scoring the LAQ

Items in Part 1 are scored for level of risk. For most items, risks range from 0 (little or no risk) to 4 (high risk) whilst some are dichotomous. Part I is scored by adding up the level of risk. The total possible score on Part I is 73. Higher scores are assumed to be associated with higher risks of disease and lower quality of life. In Part 11, a four point Likert scale ranging from 0 (almost never) to 3 (almost always) was used to assess the person's cognitive appraisal of life pressures and demands. Items are added directly and high scores indicate higher perceived levels of stress. The total possible score for Part I1 is 75.

Please circle the appropriate number

1. (a) Have you ever regularly smoked cigarettes?

No 0 Yes 1

(b) Do you presently smoke cigarettes?

No 0 Yes 3

* If you presently smoke – answer Questions 2 & 3. If not - go to Q. 4.

2. How frequently do you smoke?

Only socially (once a week or less) I

Once or twice a day 2

Up to 10 a day 3

More than 10 a day 4

3. Have you ever attempted to give up smoking?

Never 1 Yes, but have not been successful 2

4. Systolic blood pressure (mmHg) ..... Syst.

Less than 130 0

130 - 139 1

140 - 149 2

150 - 159 3

160 + 4

5. Diastolic blood pressure (mmHg) ..... Diast.

Less than 80 0

80 - 84 1

85 - 89 2

90 – 95 3

95 + 4

6. Body Mass Index

Height (without shoes) ..... cm

Weight (light clothes/no shoes ... kilos

Less than 20 1

20 – 24 0

7. Do you drink alcohol?

No, or up to 2 drinks per day 0

3 - 4 drinks per day I

5 - 8 drinks per day 2

9 - 15 drinks per day 3

More than 16 drinks per day 4

8. Do you take any drugs or medication other than tea, coffee, alcohol and nicotine (eg. Sleeping tablets, anti-anxiety drugs such as Valium, anti-depressants, hallucinogens, barbiturates, pain-killers, etc.)?

No 0

Only once or twice a year 1

Once or twice a month 2

Once or twice a week 3

Every day 4

9. Does anyone in your immediate family (father, mother, brother, sister) have a history of:

Heart disease No 1 Yes 1

Cancer No 0 Yes 1

High blood pressure No 0 Yes 1

10. How often do you exercise or go for a walk? (For at least 15 minutes each time)

3 or more times a week 0

About once a week 1

About once a month 2

Not at all 3

11. How frequently do you participate in an activity or recreation you enjoy (eg. gardening, reading, hobbies, sport etc.)?

Every day 0

Once a week 1

Once a month 2

Not at all 3

12. How often do you do any relaxation exercises?

At least once a week 0

About once a month 1

Not at all 3

13. How frequently do you eat a meal that is composed of a mixture of vegetables, fruit, bread, and lean meat?

Once every 6 months 2

At least once a day 0

14. How often do you eat fatty or sweet foods (such as fat on meat, pies, fried foods, cheeses, full cream products, chocolate etc.)?

Once or twice a week 0

About once a day 1

A few times each day 2

At least 4 times a day 3

15. Do you have close friends and family to help you with problems?

Often available 1

Sometimes available 2

Rarely or never available 3

16. How often do you give and receive affection?

Always available 0

Frequently each day 0

Occasionally each day 1

Rarely or never 4

17. In the last 6 months, how many major stressful events have you experienced (such as any experiences that cause upset or create pressure, eg. loss of a loved one, divorce, financial crisis, illness, robbery, loss of employment, accident etc.)?

None 0

1 - 2 1

3 - 6 2

7-12 3

More than 12 4

18. Do you, at present suffer from any chronic disease or illness (such as cancer, heart disease, asthma, diabetes, arthritis, etc.)?

No 0

Yes 2

If yes please list the disease(s) .....

19. Do you suffer from physical symptoms (such as headache, backache, poor appetite, dizziness, sleep disturbance, loss of sexual interest, nausea, fatigue etc.)?

Not at all 0

A few times a year 1

Once or twice a month 2

Once or twice a week 3

Every day 4

If yes, please list these symptoms

20. How often do you have a good night sleep?

Most nights 0

About every second night 1

About once a week 2

Rarely 3

21. Do you drink tea or coffee?

No, or up to 3 cups per day 0

4 - 8 cups per day I

9 - 12 cups per day 2

13 - 20 cups per day 3

More than 20 cups per day 4

		Factor I loading
1.	My life is controlled by luck and chance	.36
2.	I feel nervous and not in control	.67
3.	I worry too much about things	.66
4.	I have difficulty making decisions	.55
5.	For me, it is a waste of time exercising and relaxing	.36
6.	It is better to avoid life's pressure than face them	.38
7.	There is not much I can do to solve my problems	.49
8.	I get stressed very easily	.70
9.	Managing my time is difficult	.52
10.	It is difficult to concentrate on what I am doing	.58
11.	I have no confidence in what I do	.43
12.	I feel things are getting on top of me	.65
13.	I cannot control the stress I experience	.65
14.	My work causes me to become stressed	.50
15.	I am not satisfied with the way I am managing my life	.59
16.	I feel angry and frustrated	.65
17.	I get very upset when I fail to achieve what I want	.57
18.	I 'bottle up' my feelings	.42
19.	I try to do too many things at once	.36
20.	I get impatient with life	.59
21.	I feel guilty when I take 'time-out' to enjoy myself	.37
22.	I am not confident about managing my future	.61
23.	Other people cannot help me manage my stress	.40
24.	I am unable to enjoy my day-to-day activities	.56
25.	At the end of the day I have been feeling very hassled	.63

Appendix D

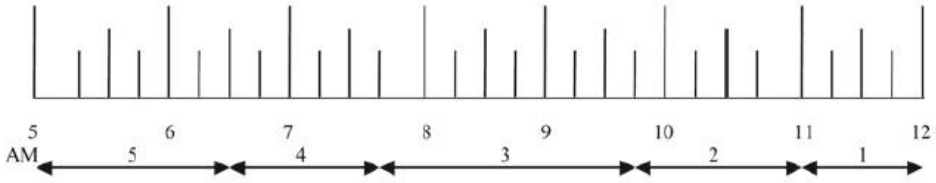
Horne-Ostberg Morningness– Eveningness Questionnaire (MEQ)

Instructions:

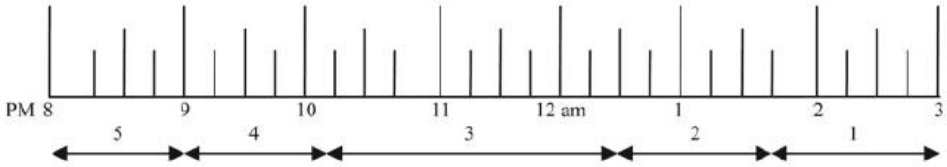
1. Please read each question very carefully before answering.
2. Answer ALL questions
3. Answer questions in numerical order.
4. Each question should be answered independently of others. Do NOT go back and check your answers.
5. All questions have a selection of answers. For each question place a cross alongside ONE answer only. Some questions have a scale instead of a selection of answers. Place a cross at the appropriate point along the scale.
6. Please answer each question as honestly as possible. Both your answers and the results will be kept, in strict confidence.
7. Please feel free to make any comments in the section provided below each question.

The Questionnaire with scores for each choice

1. Considering only your own "feeling best" rhythm, at what time would you get up if you were entirely free to plan your day?



2. Considering only your own "feeling best" rhythm, at what time would you go to bed if you were entirely free to plan your evening?



3. If there is a specific time at which you have to get up in the morning, to what extent are you dependent on being woken up by an alarm clock?

Not at all dependent ☐ 4
Slightly dependent ☐ 3
Fairly dependent ☐ 2
Very dependent ☐ 1

4. Assuming adequate environmental conditions, how easy do you find getting up in the mornings?

Not at all easy ☐ 1
Not very easy ☐ 2
Fairly easy ☐ 3
Very easy ☐ 4

5. How alert do you feel during the first half hour after having woken in the mornings?

Not at all alert ☐ 1
Slightly alert ☐ 2
Fairly alert ☐ 3
Very alert ☐ 4

6. How is your appetite during the first half-hour after having woken in the mornings?

Very poor ☐ 1
Fairly poor ☐ 2
Fairly good ☐ 3
Very good ☐ 4

7. During the first half-hour after having woken in the morning, how tired do you feel?

Very tired	☐ 1
Fairly tired	☐ 2
Fairly refreshed	☐ 3
Very refreshed	☐ 4

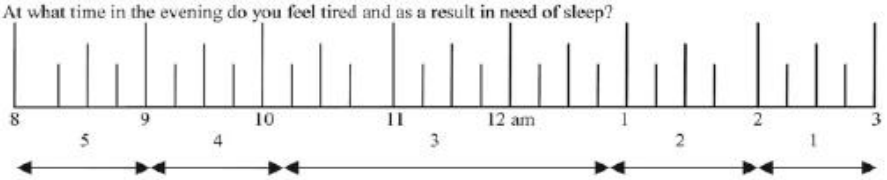
8. When you have no commitments the next day, at what time do you go to bed compared to your usual bedtime?

Seldom or never later	☐ 4
Less than one hour later	☐ 3
1-2 hours later	☐ 2
More than two hours later	☐ 1

9. You have decided to engage in some physical exercise. A friend suggests that you do this one hour twice a week and the best time for him is between 7:00-8:00 a.m. Bearing in mind nothing else but your own "feeling best" rhythm, how do you think you would perform?

Would be on good form	☐ 4
Would be on reasonable form	☐ 3
Would find it difficult	☐ 2
Would find it very difficult	☐ 1

10. At what time in the evening do you feel tired and as a result in need of sleep?



11. You wish to be at your peak performance for a test which you know is going to be mentally exhausting and lasting for two hours. You are entirely free to plan your day and considering only your own "feeling best" rhythm which ONE of the four testing times would you choose?

8:00-10:00 a.m.	☐ 6
11:00 a.m.-1:00 p.m.	☐ 4
3:00-5:00 p.m.	☐ 2
7:00-9:00 p.m.	☐ 0

12. If you went to bed at 11 p.m. at what level of tiredness would you be?

Not at all tired	☐ 0
A little tired	☐ 2
Fairly tired	☐ 3
Very tired	☐ 5

13. For some reason you have gone to bed several hours later than usual, but there is no need to get up at any particular time the next morning. Which ONE of the following events are you most likely to experience?

Will wake up at usual time and will NOT fall asleep	☐ 4
Will wake up at usual time and will doze thereafter	☐ 3
Will wake up at usual time but will fall asleep again	☐ 2
Will NOT wake up until later than usual	☐ 1

14. One night you have to remain awake between 4-6 a.m. in order to carry out a night watch. You have no commitments the next day. Which ONE of the following alternatives will suit you best?

Would NOT go to bed until watch was over	☐ 1
Would take a nap before and sleep after	☐ 2
Would take a good sleep before and nap after	☐ 3
Would take ALL sleep before watch	☐ 4

Appendix E

The Epworth Sleepiness Scale (ESS)

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g. a theatre or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car, while stopped for a few minutes in the traffic	

Appendix F

Pittsburgh Sleep Quality Index

Subject's Initials_____ID#_____Date_____Time_____AM PM

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

Appendix G

Approach email

Participate in a research study looking into the effects of light on human sleepiness and alertness

Dear QUT staff and students,

My name is Shamsi Shekari Soleimanloo from the Centre for Accident Research and Road Safety – Queensland (CARRS-Q). I am doing a PhD into the effects of light on human sleepiness and alertness under supervision of Associate Professor Simon Smith. Sleepiness is a major contributor of road crashes, and conducting research in this area is important to help us understand how to combat driver sleepiness.

We are seeking people aged 18-25 years old to take part in our study. The study will require you to be involved for two weeks, and the requirements are as follows.

Week 1- During the first week you can:

Sleep for 8 hours each night; however

Sleep must occur between 11pm and 7am.

Week 2- During the second week you will be required to:

Gradually reduce your sleep time by 1 hour (i.e. 15 mins less for 4 nights, resulting in the final sleep time of 11pm to 6am);

attend 3 consecutive testing sessions at the Institute of Health and Biomedical Innovation, QUT, Kelvin Grove (60 Musk Avenue, Q-Block – IHBI). These sessions will take a total of 9 hours, and involve:

Chewing either caffeinated or decaffeinated chewing gum;

Wearing special light-emitting glasses that emit either blue or red light;

Simulated driving tests; and

Computerised reaction time test

Moreover, you may experience sleepiness symptoms such as poor concentration, head nodding during few days prior to testing, sleepiness during testing sessions, and potential increased sleep duration for 2-3 days after completion of the study. To compensate you for your time, we will provide you with $150 and taxi vouchers for travel to and from the laboratory.

Please view the attached recruitment flyer for further details on the study and how to participate. Should you wish to participate or have any questions, please contact us via phone or email.

Please note that this study has been approved by the QUT Human Research Ethics Committee (approval number (1300000846).

Many thanks for your consideration

Principal Researcher:

Shamsi Shekari Soleimanloo

PhD Student

Centre for Accident Research and Road Safety- Queensland

Queensland University of Technology

Phone: 3138 0137

Email: s.shekarisoleimanloo@qut.edu.au

Associate Researcher:

Associate Professor Simon Smith

Principal Research Fellow

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Queensland University of Technology

Phone: 3138 4908

Email: simon.smith@qut.edu.au

Appendix H

Participant Recruitment Flyer

Queensland University of Technology Brisbane Australia	**PARTICIPATE IN RESEARCH** **Information for Prospective Participants**

The following research activity has been reviewed via QUT arrangements for the conduct of research involving human participation.
If you choose to participate, you will be provided with more detailed participant information, including who you can contact if you have any concerns.

Effects of light on human sleepiness and alertness: A simulated driving experiment

Research team contacts

Principal Researcher: Mrs Shamsi Shekari Soleimanloo

Associate Researcher: Associate Professor Simon Smith

Centre for Accident Research & Road Safety – Queensland (CARRS-Q) – Queensland University of Technology (QUT)

What is the purpose of the research?

The purpose of this project is to assess the impact of mild sleepiness on young drivers' alertness and performance, and to assess the nature and magnitude of the alerting effects of light on drivers' sleepiness and performance while driving.

Are you looking for people like me?

The research team is looking for people aged 18-25 years, who hold a driver's licence with no physical restrictions to drive, and normal vision (including normal vision while using spectacles and or contact lenses).

You are *not* eligible for this study:

- If you are a professional driver, shift worker or have travelled overseas in the past month.
- If you usually go to sleep after 12am (midnight).
- If you have any significant health problems, particularly if you suffer from vestibular and/or psychiatric diseases.
- If you have any eye or optic nerve diseases affecting your normal vision, such as retinopathy, colour vision that is incompatible with driving, and diseases of the optic nerve or ocular media.
- If you take prescription medication or illicit drugs
- If you do not consume caffeine or are a heavy caffeine user (e.g. drink more than 3 caffeinated drinks per day).
- If you consume more than 2 standard alcoholic drinks per day (a standard drink contains 10 grams of alcohol).

What will you ask me to do?

If you are interested in this study please send an email to the researcher. The researcher will email you a Participant Information Package to let you know about the nature of this research and the inclusion criteria. If you are still interested in participating in this study after consideration of the information provided in the Participant Information Package, we request you contact the research team by email or phone to advise them of your interest. You will then be contacted by phone to

confirm you meet the initial inclusion criteria (as mentioned above), and a time will be arranged for you to attend the screening session in a laboratory at the Institute of Health & Biomedical Innovation (IHBI), QUT, Kelvin Grove.

During this session the researcher will complete a battery of questionnaires. If you meet the eligibility criteria, you will be given an Actiwatch (a small wrist-watch device that records your activity levels and allows us to monitor your sleep) and advised of when you need to wear the Actiwatch, as well as when the subsequent testing sessions will take place. You will be required to wear the Actiwatch for two weeks prior to the commencement of your testing sessions. During the first week, you will be asked to sleep between 11pm and 7am each night. At the start of the second week, you will be asked to reduce your sleep by 15 minutes for 4 nights, resulting in sleep loss of an hour (thus sleeping between 11pm and 6am). In the final three days of the second week, you will be asked to attend three testing sessions in the laboratory at IHBI (one testing session per day). Each testing session will take about 3 hours (i.e. approximately 8:10am to 11am).

During the testing sessions sensors will be stuck on your scalp, using a non-toxic sticky gel, to measure your brain waves and on your chest to measure your heart rate. You will also be required to chew either caffeinated or decaffeinated chewing gum. Your eyes will also be exposed to either blue or red light through special light-emitting glasses. In addition, you will undertake computerised tests, including a simulated driving test and a reaction time test. In total, the 3 testing sessions will take up about 9 hours of your time across the 3 days.

Are there any risks for me in taking part?

There are some minor risks associated with your participation in this project. You might find the study tiring, feel sleepy or uncomfortable from the electrodes. You may experience minor eye strain, a headache, nausea or feel stimulated from exposure to low-level lights. Moreover, you may experience sleepiness symptoms such as poor concentration, head nodding during few days prior to testing, sleepiness during testing sessions, and potential increased sleep duration for 2-3 days after completion of the study. While the degree of sleepiness induced by the sleep time manipulation is likely to be *mild*, you may feel excessive sleepiness while working or studying. Therefore, you should not engage in safety-sensitive tasks such as driving. If you experience these symptoms please let us know.

If you feel stressed, very sleepy or very tired we will discuss some mitigation strategies with you. To minimize the risks of driving while sleepy, we will provide taxi vouchers for your transportation to and from the test sessions. It should be noted that if you do agree to participate, you can withdraw from participation at any time during the project without comment or penalty.

Are there any benefits for me in taking part?

It is not expected that this project will benefit you directly. However, it may benefit others in the future. We expect that the results of this study will lead to better understanding of the problem of sleepy driving, and potentiality for light as an effective countermeasure.

Will I be compensated for my time?

As you will be required to spend four sessions in the laboratory (one screening session and three test sessions), and to wear an Actiwatch for two weeks, we would like to compensate you for your time. If the screening session excludes you from the study, you will receive $20 to compensate you for your time. If you are recruited, you will receive $150 at the end of the study. Taxi vouchers for transportation to and from the laboratory will also be provided.

I am interested – what should I do next?

If you would like to participate in this study, please contact one of the research team members for details of the next step.

Ms Shamsi Shekari Soleimanloo Phone: 3138 0137
s.shekarisoleimanloo@qut.edu.au
Associate Professor Simon Smith Phone: 3138 4908
simon.smith@qut.edu.au

You will be provided with further information to ensure that your decision and consent to participate is fully informed.

Thank You!

QUT Ethics Approval Number: 1300000846

Appendix I

Participant Information Sheet

Queensland University of Technology Brisbane Australia	PARTICIPANT INFORMATION FOR QUT RESEARCH PROJECT
Effects of light on human sleepiness and alertness: A simulated driving experiment **QUT Ethics Approval Number 1300000846**	

Principal Researcher: Ms Shamsi Shekari SoleimanlooPhD student

Associate Researchers: Associate Professor Simon Smith Principal Research Fellow and Primary Supervisor

Centre for Accident Research & Road Safety – Queensland (CARRS-Q)

Dr Melanie White Senior Lecturer and Associate Supervisor

School of Psychology and Counselling, Faculty of Health

Dr Veronica Garcia Hansen Senior Lecturer and Associate Supervisor

School of Design, Creative Industries Faculty

Queensland University of Technology (QUT)

RESEARCH TEAM

Description

Sleep loss in the main cause of driver sleepiness. Young drivers are particularly vulnerable to sleep deprivation, so they are at a greater risk when it comes to sleep-related crashes and fatalities. It is not known exactly why sleepiness causes such a problem for driving and how to reduce sleepy driving. *Bright light* has been shown to have some alerting and stimulating effects, similar to caffeine, which is better known for its alerting effect. The purpose of this project is to assess the impact of mild sleepiness on young drivers' alertness and performance, and to assess the alerting effects of light and caffeine on sleepiness and driving performance

This project is being undertaken by PhD student Ms Shamsi Shekari Soleimanloo from CARRS-Q under the supervision of Associate Professor Simon Smith, Dr Melanie White and Dr Veronica Garcia Hansen. The research team is looking for people aged 18-25 years, who hold a driver's licence with no physical restrictions to

drive, and normal vision (including normal vision while using spectacles and or contact lenses).

You are *not* eligible for this study:

If you are a professional driver, shift worker or have travelled overseas in the past month.

If you usually go to sleep after 12am (midnight),

If you have any significant health problems, particularly if you suffer from vestibular and/or psychiatric diseases,

If you have any eye or optic nerve diseases affecting your normal vision, such as retinopathy, colour vision that is incompatible with driving, and diseases of the optic nerve or ocular media,

If you take prescription medication or illicit drugs,

If you do not consume caffeine *or* are a heavy caffeine user (e.g. drink more than 3 caffeinated drinks per day),

If you consume more than 2 standard alcoholic drinks per day (a standard drink contains 10 grams of alcohol; see Figure 1).

Participation

Participation in this study comprises three parts: (1) Recruitment and Screening session, (2) Actigraphy, and (3) Testing sessions in the lab

Recruitment and Screening session

This Participant Information Sheet and Consent Form is part of the Participant Information Package. This package also includes a questionnaire battery including the Pittsburgh Sleep Quality Questionnaire, the Epworth Sleepiness Scale, and the Horne-Ostberg Morningness–Eveningness Questionnaire. The questionnaire battery informs you of the types of questions you will be asked in the screening session, and allows the research team to assess your habitual sleep patterns and daytime sleepiness.

If you are still interested in participating in this study after consideration of the information provided in the Participant Information Package, we request you contact the research team by email or phone to advise them of your interest to the screening call. You will then be contacted by phone to confirm you meet the initial inclusion criteria (as mentioned above), and a time will be arranged for you to attend the main screening session.

The main screening session will take place in the desktop driving simulator laboratory (Room Q.629) at the Institute of Health & Biomedical Innovation (IHBI), QUT Kelvin Grove campus. During the screening session, the researcher will explain the study to you, obtain your written consent to participate in the study, and complete a battery of questionnaires. If you meet the eligibility criteria, you will be given an the Actiwatches (a small wrist-watch device that records your activity levels and

allows us to monitor your sleep; see Figure 2) and advised of when you need to wear the Actiwatches, as well as when your subsequent testing sessions will take place.

Actigraphy

You will be required to wear the Actiwatches for two weeks prior to the commencement of your testing sessions. During the first week, you will be asked to sleep between 11pm and 7am each night. At the start of the second week, you will be asked to reduce your sleep by 15 minutes for 4 nights, resulting in sleep loss of an hour (thus sleeping between 11pm and 6am). The e Actiwatches is a waterproof device and **must be worn day and night** during this period, including when showering, bathing and swimming. In the final three days of the second week, whilst still wearing the Actiwatches, you will be asked to attend three testing sessions in the desktop driving simulator laboratory at IHBI. Your scheduled sleep-wake timeline over two weeks of Actigraphy has been shown in Figure3.

Testing sessions in the lab

As mentioned, in the final three days of the second week of the study, you will be asked to attend three testing sessions in the laboratory at IHBI (one testing session per day). On each test day you will be required to wake up at 6am and arrive at the laboratory at 8:30am. Each testing session will take about 3 hours (i.e. approximately 8:30am to 11:15am). In total, the 3 testing sessions will take up about 9 hours of your time across the 3 days.

During the testing sessions sensors will be stuck on your scalp, using a non-toxic sticky gel, to measure your brain waves and on your chest to measure your heart rate. During the sessions you will be sitting in a quiet and dim lit environment. You will be required to chew either caffeinated or decaffeinated chewing gum, which will be undistinguishable to you. You will also be required to wear special light-emitting glasses (Re-Timer glasses; see Figure 4). This device will direct a low-level green-blue or red light onto your eyes. In addition, you will undertake computerized tests, including a simulated driving test and a reaction time test. The computerized driving test requires you to drive on a simulated road for about half an hour allowing assessment of your driving performance. The *PEBLE psychomotor vigilance task* is a simple computerized reaction time task, re-specified to measure your sleepiness and arousal. During this test a stimulus appears on the computer screen and you are required to respond as quickly as possible by pressing the spacebar. Additionally, you will be asked to rank your perceived level of sleepiness. Importantly, we ask you to refrain from consuming caffeine or taking naps on the three test-session days.

Your participation in this project is entirely voluntary. If you do agree to participate, you can withdraw from participation at any time during the project without comment or penalty. Your decision to participate will in no way impact upon your current or future relationship with QUT (for example your grades).

Expected benefits

It is not expected that this project will benefit you directly. However, it may benefit others in the future. We expect that the results of this study will lead to better understanding of the problem of sleepy driving, and potentiality of light as an effective countermeasure. As you will be required to spend four sessions in the laboratory (one screening session and three test sessions), and to wear an Actiwatch for two weeks, we would like to compensate you for your time. If the screening session excludes you from the study, you will receive $20 to compensate you for your time. If you are recruited, you will receive $150 at the end of the study. Taxi vouchers for transportation to and from the laboratory will also be provided.

Risks

There are some minor risks associated with your participation in this project. You might find the study tiring, feel sleepy or uncomfortable from the electrodes. You may experience minor eye strain, a headache, nausea or feel stimulated from exposure to low-level lights. Moreover, you may experience sleepiness symptoms such as poor concentration, head nodding during the day prior to testing, sleepiness during testing sessions, and potential increased sleep duration for 2-3 days after completion of the study. While the degree of sleepiness induced by the sleep time manipulation is likely to be *mild*, you may feel excessive sleepiness while working or studying. Therefore, you should not engage in safety-sensitive tasks such as driving. If you experience these symptoms please let us know.

If you feel stressed, very sleepy or very tired we will discuss some mitigation strategies with you. To minimize the risks of driving while sleepy, we will provide taxi vouchers for your transportation to and from the test sessions. It should be noted that if you do agree to participate, you can withdraw from participation at any time during the project without comment or penalty.

Privacy and confidentiality

All comments and responses will be treated confidentially. The names of individual persons are not required in any of the responses, and you will not be identified in any publications resulted from this study. Any data collected as part of this project will be stored securely as per QUT's Management of research data policy.

Please note that non-identifiable data collected in this project may be used as comparative data in future projects or stored on an open access database for secondary analysis.

After completion of the study, you will be advised of the type of gum you received during each session. You will also be advised of some sleepiness mitigation strategies after each test session and for use over the few days upon completion of the study. Additionally, for more information on the results of this study, you may request this information from the research team.

Consent to Participate

We would like to ask you to sign a written consent form (enclosed) to confirm your agreement to participate.

Questions / further information about the project

If have any questions or require further information please contact one of the research team members below.

Mrs Shamsi Shekari Soleimanloo	Assoc. Prof. Simon Smith	Dr Melanie White	Dr Veronica Garcia Hansen
3138 0137	3138 4908	3138 4714	3138 1623
s.shekarisoleimanloo@qut.edu.au	simon.smith@qut.edu.au	melanei.white@qut.edu.au	v.garciahansen@qut.edu.au

Concerns / complaints regarding the conduct of the project

QUT is committed to research integrity and the ethical conduct of research projects. However, if you do have any concerns or complaints about the ethical conduct of the project you may contact the QUT Research Ethics Unit on 3138 5123 or email ethicscontact@qut.edu.au. The QUT Research Ethics Unit is not connected with the research project and can facilitate a resolution to your concern in an impartial manner.

Thank you for helping with this research project. Please keep this sheet for your information.

Figure I 1 Number of standard drinks in beer, wine and spirits

Figure I 2 Philips Respironics The Actiwatches®- 2 adopted from http://www.healthcare.philips.com/main/homehealth/sleep/the Actiwatches/default.wpd

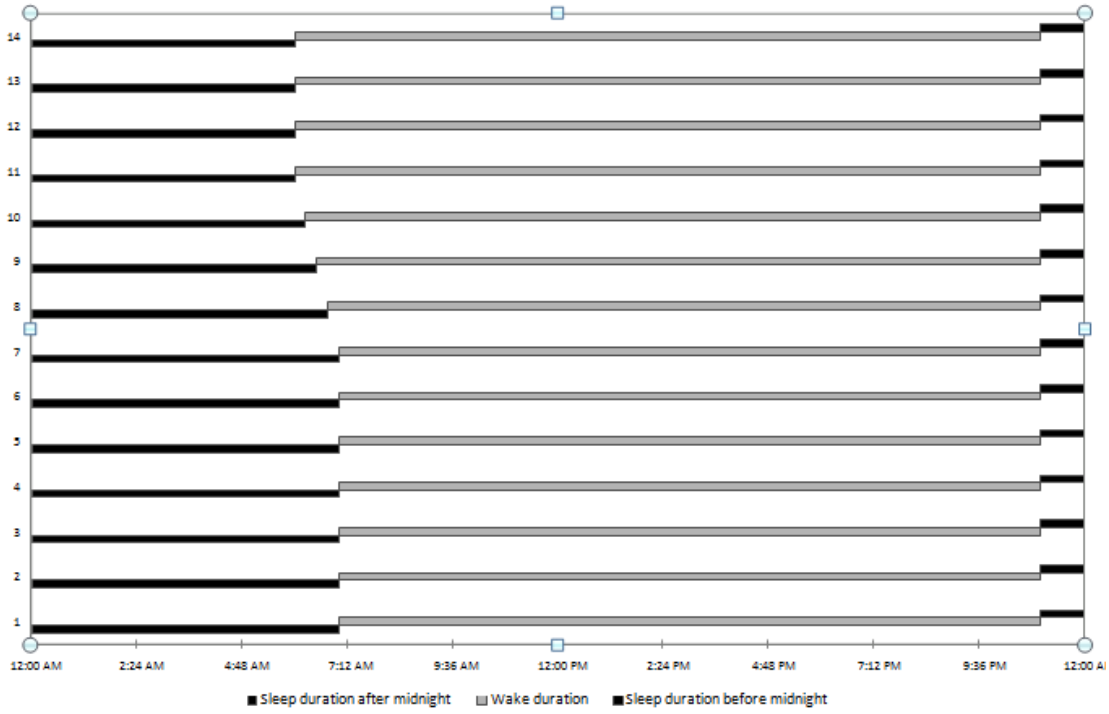

Figure I 3: Participant sleep-wake timeline over a 14-day Actigraphy period

Figure I 4: Re-Timer light glasses with USB port to be recharged, adopted from http://www.cpapaustralia.com.au/shopping/re-timer-light-glasses.html

Appendix J

Consent form

Queensland University of Technology Brisbane Australia	**CONSENT FORM FOR QUT RESEARCH PROJECT**

Effects of light on human sleepiness and alertness: A simulated driving experiment

QUT Ethics Approval Number 1300000846

RESEARCH TEAM CONTACTS

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STATEMENT OF CONSENT

By signing below, you are indicating that you:

- Have read and understood the information document regarding this project.
- Have had any questions answered to your satisfaction.
- Understand that if you have any additional questions you can contact the research team.
- Understand that you are free to withdraw at any time, without comment or penalty.
- Understand that you can contact the Research Ethics Unit on 3138 5123 or email ethicscontact@qut.edu.au if you have concerns about the ethical conduct of the project.
- Understand that non-identifiable data collected in this project may be used as comparative data in future projects.
- Agree to participate in the project.

Name .....

Signature .....

Date .....

Appendix K

Sleep-wake diary

Study day	Date	sleep time (pm)	Wake time (am)	First test session	Second test session	Third test session	Alcohol intake	Coffee intake	Breakfast intake
1	11/09/2014	11	7:00						
2	12/09/2014	11	7:00						
3	13/09/2014	11	7:00						
4	14/09/2014	11	7:00						
5	15/09/2014	11	7:00						
6	16/09/2014	11	7:00						
7	17/09/2014	11	7:00						
8	18/09/2014	11	6:45						
9	19/09/2014	11	6:30						
10	20/09/2014	11	6:15						
11	21/09/2014	11	6:00						
12	22/09/2014	11	6:00	8:30 am					
13	23/09/2014	11	6:00		8:30:00 am				
14	24/09/2014	11	6:00			8:30:00 am			

Appendix L

Screening Session Checklist

Participant name:

Preparation			
Screening Session Checklist Items	**Yes**	**No**	**Comments**
Has the time and venue of screening session been communicated with the participant?			
Is there ample time allotted for the screening to ensure that all agenda items can be sufficiently discussed?			
Has the inclusion-Exclusion checklist been prepared?			
Has the battery of questionnaires been prepared?			
Has standard drink chart been prepared?			
Has the power point slide for sleep-wake monitoring been prepared?			
Has the The Actiwatches been charged and set up one day before screening session?			
Has simulator training file been prepared?			
Has reaction time test been prepared for training?			
Has a folder for participant handouts been prepared?			
Has $20 been put in an envelope?			
Has a partial payment receipt been prepared?			
Has the participant consent form been prepared?			
Has the “Participant Actigraphy and Wakeup Message Sheet” been prepared?			
Has participant sleep wake diary been prepared?			
Has a copy “Actigraph important notes” been prepared?			

Has the name of participant been included in "Actigraphy and test calander"?			
Has a taxi voucher been prepared for the participant?			
Has the lab environment been prepared and cleaned?			
Have some cold water, instant coffee and biscuits been prepared?			
Has the note for lab door "Participant Screening in Progress, Please Do Not Disturb" been prepared and attached to the door?			
Execution			
Screening Session Checklist Items	**Yes**	**No**	**Comments**
Is the participant at ease and comfortable within the screening setting?			
Has the participant been provided with an opportunity to ask questions during screening session?			
Have the objectives of screening session been restated using PowerPoint slides?			
Has Part A in "Inclusion-Exclusion Checklist for Screening Session" been filled out?			
Have the battery of questionnaires been filled out?			
Has Part B in "Inclusion-Exclusion Checklist for Screening Session" been filled out?			
Is the participant eligible for the study?			
If participant is not eligible, have you given them $20?			
If participant is eligible, have the PowerPoint slides been explained to them?			
Has participant signed "the participant consent form"?			
Has participant been trained on how to drive on the simulator?			
Has participant been trained on how to do reaction time test?			
Has the participant been provided with a fully charged Actigraph?			
Has "Actigraph important notes" been explained to the participant?			
Has the "Participant Actigraphy and Wakeup Message Sheet" been signed by participant?			

Has start time of Actigraphy been specified for participant?			
Has the participant's sleep wake diary scheduled based on Actigraphy start time?			
Has the commuting method of participant been asked?			
Conclusion			
Screening Session Checklist Items	**Yes**	**No**	**Comments**
Has a copy of table of sleep-wake diary been given to the participant?			
Has a copy of important notes about Actigraph been given to the participant?			
Has a copy of PowerPoint slides been given to the participant?			
Has a copy of participant consent form been given to the participant?			
Has participant signed partial payment receipt?			
Has the Actiwatch been given to the participant?			
Have the start time of Actigraphy and test sessions were finalized with the participant?			
Is the time of texting to the participants for testing their wakefulness been finalized with the participant?			
If participant needs taxi for test sessions, has a taxi voucher been given to the participant?			
Has the interventional conditions for participant been counterbalanced?			
Has the road scenarios for test sessions been counterbalanced?			

Appendix M

Test Session Checklist

Participant name:

Preparation			
Test Session Checklist Items	**Yes**	**No**	**Comments**
Has the time and venue of test session been communicated with the participant?			
Has the participant been advised on washing their heir with only shampoo not conditioner?			
Has the Karolinska Sleepiness Scale been prepared?			
Has the KSS recording sheet been prepared?			
Has a total/withdraw payment receipt been prepared?			
Has the notice "Study in progress, please do not disturb" been prepared?			
Have batteries of Somte data recorder been fully charged?			
Have all material for EEG and ECG setup been prepared?			
Have red-light and blue-green- light Re-Timer glasses been charged?			
Have caffeinated and decaffeinated chewing gum pills been prepared?			
Have Philip Living Colour lights been prepared for red light less than 10 lux?			
Has $150 been put in an envelope?			
Have the scenario and configuration files been prepared?			
Has the "Participant Actigraphy and Wakeup Message Sheet" been prepared?			
Has PEBLE PPVT test been prepared?			
Has neutral filter been installed on the simulator screen?			
Has a taxi voucher been prepared for the participant?			

Has the lab environment been prepared and cleaned?			
Have some cold water, instant coffee and biscuits been prepared?			
Have randomized scenario and test condition been specified for this test session?			
Has a folder to save participant Actigraphic data been specified?			
Has a folder to save participant polysomnographic data been specified?			
Has a folder to save participant PEBLE PPVT data been specified?			
Has a folder to save participant simulator data been specified?			
Has a table to save participant KSS data been prepared?			
Has the timetable of different tasks on test day been drawn on the whiteboard?			
Has the interventional conditions for participant been counterbalanced?			
Has the road scenarios for test sessions been counterbalanced?			
Execution			
Test Session Checklist Items	**Yes**	**No**	**Comments**
Has the participant been advised to use toilet before starting test session?			
Have both participant and researcher switched off their mobile phones?			
Have data from participant the Actiwatch been copied to a specific folder in the Actiware?			
Is the participant at ease and comfortable within the Test setting?			
Have EEG and ECG electrodes been setup on the participant by 9 am?			
Have EEG and ECG recording been started straightaway after setup?			
Have the lights been off and Philip Living Colour lights been adjusted to red light at 9 am?			
Has participant been asked to seat on a chair for 30 min (until 9:30) under this dim red light?			

Has the participant been given a decaffeinated chewing gum after 15 min adaptation to darkness (at 9:15 am)?			
Has first round of PEBLE PPVT been recorded after 20min of darkness for 5min (at 9:20 am)?			
Have EEG and ECG been double checked to continue recording at the beginning of driving (at 9:30 am)?			
Has participant put on red-light Re-Timer glasses before simulated drive (at 9:30 am)?			
Has KSS level been asked from participant immediately before driving test (at 9:30 am)?			
Has participant driven on the randomized scenario for 30 min (from 9:30 to 10 am)?			
Has KSS level been recorded immediately after first drive (at 10 am)?			
Has second PEBLE PPVT been recorded after first drive for 5 min (at 10 am)?			
Has caffeinated or decaffeinated chewing gum pills been given to the participant based on the specific randomized test condition for this test session (at 10:05 am)?			
Has the participant worn red-light or blue-green-light Re-timer glasses after 15 min of chewing gum based on the specific randomized test condition for this test session (at 10:20am)?			
Has the participant driven their second driving scenario for 30 minutes (from 10:20 to 10:50 am)?			
Has KSS level been recorded immediately after second drive (at 10:50 am)?			
Has third PEBLE PPVT been recorded after second drive for 5 min (at 10:55 am)?			
Has EEG and ECG recording been stopped after PEBLE PPVT test (at 11 am)?			
Has EEG and ECG electrodes been removed from participant?			
Has participants head and skin been cleaned after test?			
Conclusion			
Test Session Checklist Items	**Yes**	**No**	**Comments**

Has participant been provided with some refreshment?			
Has coffee, alcohol and meal intake been restated for the participant?			
Has taxi voucher been provided for participant (if required)?			
Has participant signed complete payment receipt (in the last session)?			
Have EEG and ECG data been transferred to data manager and a backup file been copied to the hard drive?			
Have PEBLE PPVT data been stored and backup file been copied to hard drive?			
Have the simulator data been saved in the simulator data file and a backup file been copied to the hard drive?			
Has KSS data been stored in a file in hard drive?			
Have EEG and ECG electrodes been cleaned and disinfected properly?			
Has the Actiwatch been removed from participant's wrist (last session)?			
Have all preparation steps for the next test day been taken based on preparation section of this checklist?			

Appendix N

Data setup in SPSS for demographic, Actigraphic, KSS and PPVT data

Since the study design was a within subject repeated measures design, data were sorted in SPSS as below:

First codes of participants were entered in the SPSS in the order of 301 to 330. The demographic and Actigraphic data had only one measure and entered in separated columns for each participant code. As for KSS and PPVT data, first values of these data were named and labelled in the "Variable View" of SPSS. The name comprised three elements of name of variable, Condition Type (1, 2 or 3) and the time of recording KSS (1= before first drive, 2= after first drive and 3= after second drive). For example KSS 23 was assigned to the KSS variable measured with the Intervention Type 2 (light only) and after the second drive. Since the KSS and PPVT variables were recorded three times every test session, there were 9 records for the KSS and for every variable derived from PPVT for each participant in the SPSS file. All variables of the KSS and PPVT were entered in separate columns after demographic and Actigraphic data. This form of setting up the data made it possible to perform the repetitive measures, within-participants ANOVA analysis. Table N1 represents the name and the label of each KSS record.

Table N 1Naming and labelling of KSS scores in SPSS

Order of data in SPSS	Name of KSS record	Label of KSS record
1	KSS11	KSS, Condition 1, before first drive
2	KSS12	KSS, Condition 1, after first drive
3	KSS13	KSS, Condition 1, after second drive
4	KSS21	KSS, Condition 2, before first drive
5	KSS22	KSS, Condition 2, after first drive
6	KSS23	KSS, Condition 2, after second drive
7	KSS31	KSS, Condition 3, before first drive
8	KSS32	KSS, Condition 3, after first drive
9	KSS33	KSS, Condition 3, after second drive

Appendix O

Data setup in SPSS for the EEG, ECG, and driving performance outcome measures

For the EEG, ECG and driving performance outcomes, there was an average of 30-min data for each variable, each Intervention Type and each drive (30 min). Since in every test session there were two drives, a total number of 6 values for each variable for each participant were entered in consecutive columns in the SPSS. The name of each variable comprised three elements as follows:

- Name of variable
- Intervention Type (1, 2 or 3); values of Condition 1 were presented before Condition 2 and those of Condition 2 before condition 3.
- Timing of recording the variable; before receiving the intervention (first drive) or after receiving the intervention (second drive), with the number 1 representing the first drive.

To clarify the naming and setting the data in SPSS, data for the standard deviation of lateral lane position has been presented in Table O1.

Table O1: Naming and labelling of SD Lateral Lane position

Order of data	Name of variable	Label of variable
1	SDLATLANPOS11	SD of lateral lane position, Condition1, after first drive
2	SDLATLANPOS12	SD of lateral lane position, Condition1, after second drive
3	SDLATLANPOS21	SD of lateral lane position, Condition2, after first drive
4	SDLATLANPOS22	SD of lateral lane position, Condition 2, after second drive
5	SDLATLANPOS31	SD of lateral lane position, Condition 3, after first drive
6	SDLATLANPOS32	SD of lateral lane position, Condition 3, after second drive