KILLSLEEP

COUNTERMEASURES OF SLEEPINESS AT THE WHEEL AND PREDICTION OF RESPONSES ACCORDING TO INTERINDIVIDUAL DIFFERENCES

Convention 08MT S019 « Killsleep »

Effects of blue light and physical activity on the nocturnal driving performance.

Table of Contents

Short Summary

Effect of blue light and physical activity on motorway nocturnal driving

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Drowsiness caused by sleep deprivation is responsible for many traffic accidents and it becomes necessary to develop counter-measures to fight this drowsiness. Two new possibilities can be considered: the introduction of a lamp emitting a blue light in the car cockpit or the practice of moderate physical activity before driving. Indeed, exposure to blue light or performing moderate physical activity improves nocturnal vigilance.
Within this project, two studies have been conducted to verify the effect of continuous exposure to blue light and to verify the effect of 20 minutes of moderate physical activity performed before driving on the nocturnal performance in young and mature people deprived of sleep. The effects of these two potential counter-measures were compared in a randomized and controlled way to a well-recognized counter-measure (taking 200 mg of caffeine) or placebo (decaffeinated coffee). The study of the effect of blue light was conducted in ecological condition (actual driving on a motorway) and the study of the effect of physical activity was conducted on a driving simulator.
Continuous exposure to blue light improves nighttime driving ability as well as a caffeine intake in all age's subjects. Continuous exposure to blue light is an embedded and preventive countermeasure to drowsy driving induced by sleep deprivation. Moderate physical activity performed before driving improves nocturnal performance in mature subjects. However physical activity reduces nocturnal driving performance in young subjects. Both occasionally tested countermeasures do not affect sleep following exposure.
Further studies are needed to increase the tolerance of blue light and validate moderate physical activity in mature individuals in ecological condition.

Summary: Effects of blue light and physical activity on the nocturnal driving performance.

Background

Our 24/24h and 7/7d working society requires more flexibility in terms of work and activities and sleep schedules. For professional or sociological reasons, people voluntarily reduce their daily hours of sleep, lengthen the duration of wakefulness and carry out activities during the night. These factors induce drowsiness that will diminish simple cognitive performance but also complex cognitive tasks such as driving.
To meet society's demands, the development and use of counter-measures to drowsiness (ie methods against), which will increase alertness and performance of car drivers, is paramount in preventing accidents related to sleepiness. Indeed, drowsy drivers should stop (the best countermeasure), but for various reasons they do not. The reasons for the subjects to continue driving are unknown and probably differ from one driver to another. Among other reasons, not to stop could be linked to security problems on the rest areas (especially for women), but also to be far from a rest area, being relatively close destination, not to see signs of decreased alertness or believe in their ability to resist to drowsiness.
In order to continue driving, drowsy drivers have developed many strategies used in an intuitive way, such as to open the window, to turn on the radio, to talk with passengers, to increase their speed or to stop for some exercise or walking (Anund et al., 2008). However opening the window or turning on the radio is not effective (these results were found in the swedish study of the KILLSLEEP project). Other strategies such as walking, napping and drinking awakening beverages are often used by drowsy drivers. Numerous studies have demonstrated the effectiveness of the nap and awakening drink on driving hypovigilance. Yet only 45% of drivers drink coffee and 18% take a nap to fight against drowsiness (Anund et al., 2008). 45% of drivers walk to fight against drowsiness but there is no study examining the effect of moderate exercise on hypovigilance. All counter-measures do not have the same effect on drivers (inter-individual effect). It is important therefore to define new counter-measures, but also to determine in which drivers they are effective. The introduction of new counter-measures involving embedded systems becomes paramount because those systems avoid the driver to stop in a non-suitable place and especially to take a counter-measure to drowsiness too late.

<u>Risks due to drowsy driving</u>

Public health studies have shown that drowsy driving and its associated risk of falling asleep are responsible for a significant number of road accidents that occur often in monotonous driving conditions: 20% of motorways accidents and near 30% of fatal truck accidents. Accidents on motorways often involve a single vehicle that drove off the road and collided with an obstacle or another vehicle without a reaction from the driver (ie absence of skid marks on the ground). These accidents generally cause serious injury or death due to a high speed at impact.
Studies have also shown that drowsy driving multiplied by 8 the risk of having an accident. Driving in the early morning and driving between 2 and 5 hours multiply by six the risk of accidents. Finally, a driver who slept 5H or less the night before his departure is three times more likely to have an accident.

Drowsy driving causes effects similar to the effects of drinking and driving. Indeed, 17 hours of prolonged wakefulness between 8 am and 3 am is equivalent to 0.5g / l of alcohol in blood and 24 hours of prolonged wakefulness (a full night without sleep) corresponds to 1g / l blood alcohol in terms of performance degradation.

Counter-measures known to fight drowsy driving

Naps and caffeine intake are currently used counter-measures that have proven effective in drowsy drivers.

Caffeine

Caffeine blocks adenosine receptors that are involved in the genesis of sleepiness. In subjects deprived of sleep, caffeine increases the cognitive and psychomotor performance and arousal capabilities. 200 mg of caffeine improves the ability to driving but also precise handling. The effect of coffee appears quickly (30 minutes) after ingestion but only lasts about 1:30 to 2:00.

Nap (sleep intake)

Sleep intake will reduce sleep pressure and thus drowsiness and cognitive performance degradation. Nap improves the ability to driving in subjects deprived of sleep. To be effective, nap should not exceed 20 to 30 minutes and should have been made half an hour before driving.

Potential counter-measures

Physical activity

Moderate exercise improves alertness, but also cognitive abilities in individuals deprived of sleep. However, some studies do not demonstrate this awakening effect. Recently, several studies have shown that physical activity could improve the ability to concentrate. But so far, few have evaluated the influence of physical activity declines in performance induced by sleep deprivation. Similarly, no study has yet been made to examine whether exercise can be used as a counter-measure to drowsy driving induced by sleep deprivation.

Blue Light

Exposure to high intensity white light has an acute awakening effect. Work studying the effect of blue light has demonstrated the beneficial effect of nocturnal exposure to blue light on the synchronization of biological rhythms, the activation of certain physiological functions as well as improving alertness and simple cognitive performance. The advantage of using blue light as a counter-measure to sleepiness is its very low intensity (5 lux) compared to white light which can be then used in a car without distracting the driver.

Inter individual differences

It has been shown that the ability to perform a nocturnal activity vary considerably from one individual to another. Thus only certain individuals do not experience real difficulties at night. Generally, nocturnal performance collapses while it is still comparable to the level of arousal in some people. Thus, it appears that some individual characteristics (such as age or cognitive

profile) or biological markers of sleep pressure (adrenergic mechanisms, genetic polymorphisms and hormone levels of cortisol and amylase) would identify drivers susceptible to sleep deprivation. The search for candidate genes for resistance to sleep deprivation is currently very promising.
The answer to counter-measures also varies from one individual to another. For example, the nap is much more effective in younger than in older subjects contrary to coffee that is both efficient in young than older subjects. However, caffeine intake improves nocturnal performance only in subjects sensitive to the effects of caffeine. The differences observed in the psychostimulant effects of coffee would be explained by a polymorphism of the gene encoding the adenosine receptors.

Experiments performed

Effect of light blue and coffee on night driving on the motorway: a study of inter-individual differences (France)

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Objectives
The main objective of this study is to determine whether exposure to blue light while driving is effective on the ability in real car in drowsy drivers.

Secondary objectives are to determine the effect of age on the effectiveness of counter-measures. To determine individual differences (cognitive, genetic and hormonal) in the degradation of neurobehavioral functions and effectiveness studied counter-measures. Finally, our goal is to determine the effects of blue light on the quantity and quality of recovery sleep (after driving).

Subjects
48 healthy male volunteers with mean age of 33.2 ± 1.6 years were included.

Method
For 3 nights separated by at least a week, each volunteer drove 400 km on a highway for 4 hours (from 1 pm to 5:15) with a break of 15 minutes at the middle. During these three nights, each volunteer was randomized to receive either continuous exposure to blue light (goLITE, wavelength: 468NM, intensity: 225µw/cm2) while driving, or 2 * 200 mg of caffeine or a placebo coffee before departure and during the break. Efficacy criteria were the number of inappropriate lateral lines crossings (FILL) and standard deviation of the position of the vehicle (vehicle stability).
These efficiency criteria are analyzed by a linear mixed model analysis.
To determine individual differences, the chronotype, subjective sensitivity to caffeine, the polymorphism of certain genes involved in regulating sleep and wakefulness PER3 are estimated or measured. To define the effect of blue light, the duration, quality and schedule of

three nights of sleep following exposure to counter-measures are objectified by recording the activity of the subjects.

Results
8 volunteers (17%) were dazzled by the blue light and could not drive. The results for the 40 other volunteers show firstly that the counter-measures improve driving performance. Continuous exposure to blue light as well as coffee reduces the number of FILL and improves vehicle stability. Genetic and hormonal measurements are being analyzed. At this stage of the analysis, we do not identify the factors that can explain the deterioration of neurobehavioral functions and effectiveness of the studied counter-measures.
Duration, sleep quality and sleep schedules of three nights after the nocturnal exposure to counter-measures are not changed.

Conclusion
Exposure to blue light, if it does not dazzle the drivers, improves the nocturnal ability to drive as much as caffeine and can therefore be used as a on-board preventive countermeasure and drowsy driving-induced sleep deprivation. Although the blue light has a synchronizing effect, this study demonstrates that sleep does not change following a bystander.

Effects of physical activity on the middle night vigilance

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Objectives
To compare the effect of 15 minutes aerobic exercise of low intensity to those of coffee (2 * 200 mg of caffeine) and of placebo of coffee on the performance of four hours of night driving in healthy young and mature. The secondary objective was to determine the effect of age on the effectiveness of counter-measures (physical activity and coffee) on driving ability.

Subjects
24 healthy subjects were recruited and divided into 2 groups of 12 young (22.4 3.2 years) and 12 mature (45.4 2.8 years).

Method
For 3 nights separated by at least a week, each volunteer drove 400 km on a driving simulator for 4 hours (1 hour to 5:15) with a break of 15 minutes in the middle. During these three nights, each volunteer has either 20 minutes of moderate physical activity prior to departure and during the break, either received 2 * 200 mg of caffeine or a placebo of coffee before departure and during the break. Efficacy criteria were the number of inappropriate line crossings (FILL) and the standard deviation of the position of the vehicle (vehicle stability). The 20 minutes of physical activity corresponded to 5 min training followed by 15 min at a constant intensity of 50% of maximal aerobic power initially obtained for each participant. Driving simulation (simulator INRETS SIM2) was performed on a very monotonous portion of motorway with no other users or events that stimulate alertness. The evaluation criteria are when driving on the one hand the number of inappropriate line crossings and also the standard deviation of lateral position of the vehicle.

These efficacy criteria were analyzed by ANOVA with 3 factors (type of subject x condition x hours of driving).

Results

Caffeine improves driving performance of mature drivers and are less important for young drivers. However, physical activity improves driving performance, only in mature subjects and is as effective as caffeine. Rather surprisingly, the physical activity at night has a deleterious effect on driving ability in young subjects. During this study on driving simulator, it appears that during night, sleep-deprived young people drive less efficiently than mature sleep deprived subjects.

Conclusion

Caffeine and exercise can dramatically improve the performance of nocturnal driving simulator in subjects mature. However the proposed physical activity degrades driving performance in young patients. Several hypotheses can be proposed to explain these results: the proposed activity would not be adequate and physical activity at night may affect alertness through sleep-wake rhythm, which would be age-dependent.

General conclusions

This research confirms that taking 200 mg of caffeine improves the ability to drive at night for 2 hours in subjects deprived of sleep. It also demonstrates that continuous exposure to blue light improves the performance of sleep-deprived drivers. To increase the tolerance of continuous exposure to blue light, new studies with a lower light intensity or a more suitable location should be performed. This result is very important because this is the first study to demonstrate the effectiveness of a on board counter-measure of performance conducted in sleep deprived subjects. The on-board counter-measures have the advantage of being non-interventional and preventive unlike caffeine intake and sleep (nap) that require in the majority of cases to stop the vehicle.

Another encouraging result shows that moderate exercise of 20 minutes improves driving performance of middle-aged subjects without sleep. However it has a reverse and deleterious effect on driving ability in young subjects.

Both counter-measures tested in this project do not change the duration, quality and sleep schedules after occasional exposure.

This study confirms that young subjects are more sensitive to the effects of sleep deprivation on performance than mature subjects. However this observation is no longer observable in ecological situation (real driving). At this stage of analysis, no other inter-individual factor has been identified.

Scientific background

Introduction

Drowsiness (Hakkanen and Summala 2000; Hakkanen and Summala 2001; Connor, Norton et al. 2002) has been identified as the reason behind fatal road crashes and many industrial accidents (Mitler, Carskadon et al. 1988). A serie of studies by the National Transportation Safety Board (NTSB) in the USA has pointed out the significance of sleepiness as a factor behind accidents involving heavy vehicles (NTSB 1990; NTSB 1995). In the NTSB study (which was very probing) the conclusion was that 52 per cent of 107 one-vehicle accidents involving heavy trucks were fatigue-related; in 17.6 per cent of the cases, the driver admitted to fall asleep (NTSB 1995).

Our 24/7 society requires more and more flexibility in terms of work, activities and sleep schedules. Work but also leisure induces voluntary reduction of daily sleep duration, extensive periods of wakefulness or activities in the circadian deep (3-5 a.m.) which are causes of sleepiness-related vehicle collisions. A study by Connor et al., showed that sleep inferior to 5 hours was associated with a doubling of the crash risk (Connor, Norton et al. 2002). Nocturnal periods of activity are major causes of sleep-related accidents. The probability of sleep-related accidents for automobile drivers is higher in the early morning (2-7am) (Horne and Reyner 1995). Driving between 21:00 am and 5:00 am increases the risk for traffic accidents by 5.6 times (Connor, Norton et al. 2002). A higher risk of accidents is related to nocturnal activity when circadian clocks and sleep pressure increase sleepiness and decrease the neurobehavioral performance. Performance assessed by simple reaction times remains stable for about 16 hr of wakefulness (Dijk, Duffy et al. 1992), and decrease thereafter to reach a dramatic impairment after 24 hr of wakefulness (Cajochen, Khalsa et al. 1999; Graw, Krauchi et al. 2004). The maximum impairment is observed 2-4 hr after the melatonin peak (Cajochen, Khalsa et al. 1999).

Because of conflicts between physiological needs and social or professional activities, developing safe and affordable countermeasures to sleepiness at the wheel is a key issue in crash prevention. Stopping the car is clearly the optimal countermeasure, yet many people continue to drive. The reason for this is unknown and probably differs between drivers. It has been shown (Anund, Kecklund et al. 2008) that counteracting sleepiness with a nap (a

presumably efficient method) was practiced by drivers with experience of sleep-related crashes or with experience of driving during severe sleepiness, as well as by professional drivers, males and drivers aged of 46-64 years old. One reason among others for not stopping could be related to safety problems at rest stops (especially for women), such as being far away from any possible rest stops, but also being relatively close to one's destination, lacking of insight regarding one's state of alertness or believing in one's superior ability to handle sleepiness.

Drivers have developed many strategies to fight sleepiness at the wheel. These strategies rely on popular beliefs such as opening the window, turning on the radio, starting a conversation with a passenger, or increasing speed and are among the most frequently used ones (Anund, Hjälmdahl et al. 2007). However, since it was not demonstrated in studies using driving simulators, these strategies do not seem to be effective, (Reyner and Horne 1998). Still, there is a possibility that combining the stimulating context of real-life driving with simple countermeasures might provide sufficient alertness to ensure safe driving. This question seems to be of considerable importance in relation to prevention of sleep-related driving accidents.

Other countermeasures, including sleeping (or napping), walking and drinking alerting beverages, such as caffeine or caffeine-containing beverages, are also very used by drivers.

Various studies showed that napping and drinking alerting beverages reduced sleepiness at the wheel. However, only 45% of drivers take a coffee and 18% nap to fight sleepiness (Anund, Kecklund et al. 2008). The effect of efficient countermeasures on nocturnal driving performance (Light Blue) still has to be tested. Another strategy to fight drowsy driving is to use embedded systems or road equipment to inform the driver of the encountered risk. These strategies are expanding rapidly, particularly for embedded systems, but require experimental studies to verify their effect on sleepiness.

Thus, drowsy driving is a major public health issue given its daily impact. The ENT Action Group 15 "drowsy driving" from the "ERANET transport" framework was established in February 2006. This group, in which Professor Philip is involved, was composed of experts from different countries (Germany, Belgium, Finland, France, Great Britain, Netherlands and Sweden). This expert group has written the European White Book "Sleepiness at the wheel"(ENTActionGroup15 2009). This White Book gives the state of knowledge on the field and proposes 2 axis of research that should be developed in the future (to identify the main

factors responsible for drowsy driving and to develop countermeasures against sleepiness at the wheel). Several countries (France, Norway, Netherlands and Sweden) have agreed to finance several projects on the epidemiology and countermeasures to sleepiness.

The French group [SANPSY - P. Philip et C. Fabrigoule (CNRS USR3413 – Bordeaux Hospital, University of Bordeaux), INSERM ERI27 "Mobility: Cognition & Temporality - D. Davenne (STAPS Dept., University of Caen) and Centre of Sleep and Alertness - D. Leger (Department of Physiology, Hôpital Hotel-Dieu, Paris)] and the Swedish group [the Stress Research Institute – T. Åkerstedt (Stockholm University, Sweden) and The Swedish Institute for Road and Transport Research – A. Anund (VTI, Linköping, Sweden)] will conduct experimental researches on the effect of countermeasures against drowsy driving (Killsleep project).

French [GENPPHASS - P. Philip (CNRS 5227 - University Hospital of Bordeaux, Bordeaux University)] and Swedish groups [the Stress Research Institute – T. Åkerstedt (Stockholm University, Sweden) and the Swedish Institute for Road and Transport Research – A. Anund (VTI, Linköping, Sweden)] will also perform a study on the role of sleepiness in highway accidents (Crashstudy project).

The Dutch group (TNO Human Factors – M. Hoedemaeker, Utrecht, Netherlands) will focus on examining how to educate the public about drowsy driving (Project Yawn).

The Norwegian group (Transportøkonomisk Institute - F. Sagberg, Oslo, Norway) will focus on the drivers experience concerning warning rumble strips (using a questionnaire) and also on a review of Fatigue Management schedules (Project Yawn).

This document presents the state of knowledge of the Killsleep project "COUNTERMEASURES IN SLEEPINESS AT THE WHEEL AND PREDICTION OF RESPONSES ACCORDING OF INTERINDIVIDUAL DIFFERENCES" whose objective is to study the effect of fresh air, radio, blue light and physical activity on nocturnal driving performance. This project will also examine the markers that allow determining the individual differences (cognitive, genetic and hormonal) in the degradation of nocturnal driving performance and in the effectiveness of the studied countermeasures. Indeed, as discussed below, the performance of each individual is not affected equally by sleep deprivation and the response to countermeasures also depends on the individual physiology. This notion of difference between individuals is strategic in the transportation field where the concepts of safety and risk prediction are a vital issue for users of systems.

Measure of Driving Ability

Driving is a complex task that implies monitoring situations, the cognitive management of various information and the implementation of effective and optimal responses to warning signals. It is therefore involving a range of visual, cognitive and motor skills. It requires an attentive waking in terms of vigilance levels to face an environment that may be changing and to be prepared for all contingencies.

The driving ability can be measured either in simulated situation or in real-life situation on closed circuit or on open road.

Driving simulation consists in giving the illusion to a driver that he is moving on a road environment and driving a vehicle. The environment and the vehicle are virtual but the control commands of the vehicle are not. Driving simulators are tools often considered as an alternative to safely test the driving ability. The driving simulator allows a strict control of experimental parameters (eg, weather or traffic density). Driving experiments with simulators permit time benefit and reduce costs compared to experiments conducted in real world. It should be noted that problems associated with immerging the subject in a virtual environment may occur (eg, the phenomenon of "simulator sickness" can cause balance loss and / or nausea). The proportion of people with "simulator sickness" is highly variable depending on the simulator (architecture), the driving situation which is simulated (highway, urban ..) and the inherent characteristics of this population (age, sex, sensitivity to motion transport, habituation to the simulator ...). In some cases, simulator sickness can reach or exceed 80%, however it is common in the range of 10-15%. [Espié, S.,(Réseau RESAT (Réseau Eveil 2007)]. Moreover, the issue of the transferability of the results obtained on simulators to those obtained in real-life situations arises. Indeed, simulation tools have limitations on physical and behavioral accuracy, which is often far from what happen in actual driving. A scientific use of simulation tools needs to verify that the trends observed on the simulator are identical with those observed in real situations (Philip, Sagaspe et al. 2005). Thus, to qualify a simulator for its use, it is necessary to calibrate it by performing comparative tests in simulated and real life situations and checking that the trends are identical. To our knowledge, to date, none of the simulators sold by commercial companies follows this recommendation. To answer this preoccupation, the VIGISIM project (Predit 2005) aims to validate a low cost simulator permitting to identify sleepiness and fatigue.

Experiments using real-life situations allow an ecological measure of the driving ability and to evaluate impairment closer to reality. It appears that real driving on motorways is the "gold standard" to determine the effect of drowsy driving.

Researchers, in the context of pharmacological protocols on drugs antihistamines or benzodiazepines, have developed a methodology for performing real driving protocols on highway (O'Hanlon and Volkerts 1986; Ramaekers and O'Hanlon 1994). A computerized camera records the path of the vehicle and calculates the number of inappropriate line crossings and the weaving index (Standard deviation of lateral position of the vehicle (SDLP)). The number of inappropriate line crossings is considered as a risk factor as epidemiological findings showed that 65% of sleep-related accidents occur after an inappropriate line crossing (Sagberg 1999). It is counted when a wheel crosses the outer edge of lateral lines (right or left) of the lane, overtaking not included. These accidents are characterized by a road exit or a collision with an obstacle with no reaction from the driver (Pack, Pack et al. 1995; Sagberg 1999). The variability of lateral position of the vehicle is a measure that quantifies the stability of the trajectory (Figure 3) (Verster, Veldhuijzen et al. 2004). This measurement, already used in quantifying the effects of alcohol, has proved to be extremely sensitive to neurocognitive impairment induced by sedative antihistamines (Ramaekers and O'Hanlon 1994).

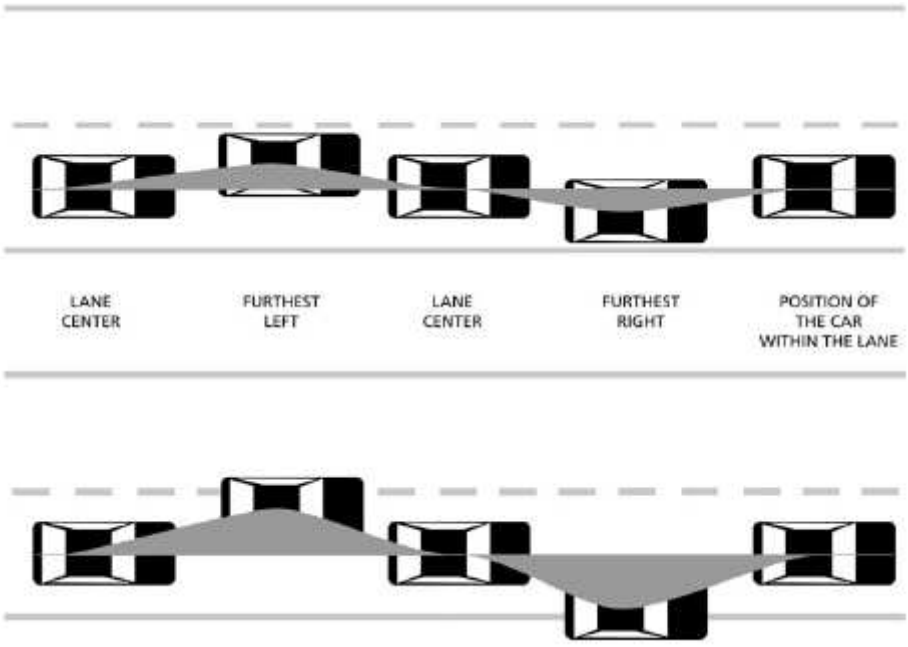

Figure 1: Meaning of the weaving index (Standard deviation of lateral position (SDLP) and inappropriate line crossings.

More recently, this methodology has been used to assess the effect of sleep deprivation and fatigue when driving on motorways. A study has shown that sleep deprived subjects (2H of sleep) versus non-sleep deprived subjects (8H of sleep) have a significant impairment of driving ability (increase in the number of inappropriate line crossings) (Philip, Sagaspe et al. 2005).

Many drivers combine extended driving, which causes fatigue and sleep deprivation (summer departures, etc.). The fatigue-related accidents occur mainly at night but no study has evaluated the relationship between driving duration and the risk of accident at night. One study performed with young healthy volunteers' showed that prolonged night driving on the highway has an impact on driving performance (Sagaspe, Taillard et al. 2008). In addition, studies have shown that driving performance was improved by the use of countermeasures to fight drowsy driving (eg, coffee, nap) (Philip, Taillard et al. 2006; Sagaspe, Taillard et al. 2007).

Countermeasure for sleepiness at the wheel knew and anticipated

1- Caffeine

Caffeine is the most used psychostimulant in our society. 2/3 of truck drivers drink coffee to fight sleepiness at the wheel during long rides (Maycock 1997). It enhances cognitive and psychomotor performance and alertness especially during sleep deprivation. However, the effect of caffeine is quick (short onset: 30 min), but brief (1h30-2h) (Quinlan, Lane et al. 1997). 100-200 mg of caffeine decrease objective (EEG) and subjective sleepiness and driving incidents (driving on simulators) in young sleepy drivers (Horne and Reyner 1996; Reyner and Horne 1998; Reyner and Horne 2000; Biggs, Smith et al. 2007). The beneficial effect of caffeine has been confirmed on driving performance in real-life driving studies (Philip, Taillard et al. 2006) and was observed in young and middle-aged subjects (Philip, Taillard et al. 2006; Sagaspe, Taillard et al. 2007).

Energy drinks (caffeine-containing beverages) reduce sleepiness and sleep-related driving incidents during monotonous driving following sleep restriction (Reyner and Horne 2002).

2- Nap

The best advice for a driver falling asleep at the wheel is to stop driving as soon as possible. The best countermeasure to sleepiness is to sleep or at least to take a nap, but only 18 % of sleepy drivers stop the car to take a break (Anund, Kecklund et al. 2008). The beneficial effect of naps on driving performance has been demonstrated in simulated conditions (Horne and Reyner 1996; De Valck, De Groot et al. 2003) and in real-life driving (Philip, Taillard et al. 2006; Sagaspe, Taillard et al. 2007).

Naps beyond 20 min can be counterproductive because they may lead to low levels of arousal and to a post-sleep "inertia" which can last for about 1-2 hours (Dinges and Barone Kribbs 1992). After napping, it is recommended to wait half an hour before driving to avoid sleep inertia. Some subjects had difficulty napping and napping is more efficient in younger than in older subjects (Sagaspe, Taillard et al. 2007). No significant benefit of 60-minute nap opportunities on driving performance measured in driving simulator in sleepy drivers was found (Lenne, Dwyer et al. 2004). Recently, one study compared the effect of a nap on young (20-30 years) and mature subjects (40-50 years) and showed that young subjects benefit more from napping than mature subjects (Sagaspe, Taillard et al. 2007).

3- Listening to radio and getting fresh air

To continue driving, sleepy drivers have developed many strategies based on popular beliefs like opening the windows (cold air on the face), turning on the radio, starting a conversation with a passenger or increasing speed (Anund, Kecklund et al. 2008). To fight sleepiness, 52 % of sleepy drivers turn on the radio and 47 % open the window (Anund, Kecklund et al. 2008). However, a study (Reyner and Horne 1998) in a driving simulator demonstrated that these two strategies provide only a temporary benefit, being only partially effective for a short period of time (about 15 minutes). That is, these strategies should not be used to prolong driving, but may provide enough time for a driver to locate and stop at a suitable place to rest. In some cases, listening to the radio can distract sleepy drivers from being aware of their sleepiness and impair driving (Reyner and Horne 1998). However, popular strategies are not tested in real situations, and it is still premature to consider these strategies as ineffective.

4- Moderate exercise

In recent decades, a growing body of literature has shown that acute physical exercise may improve the efficiency of cognitive processes. Studies suggest that a single session of physical exercise improves different aspects of cognitive function immediately after the end of the exercise period, regardless of the fitness level (Etnier, Salazar et al. 1997; Brisswalter, Collardeau et al. 2002; Tomporowski 2003). However, the literature on the relationships between acute physical exercise and cognitive function seems to provide somewhat contradictory findings. Indeed, whilst a certain number of studies indicated that short periods of physical exercise improved cognitive functioning in adults (Hancock and McNaughton 1986) others did not find any benefits (Bard and Fleury 1978; Fleury, Bard et al. 1981; Cote, Salmela et al. 1992) or even reported deterioration of cognitive function (Wrisberg and Herbert 1976; Isaacs and Pohlman 1991; Cian, Barraud et al. 2001). Although much of the evidence suggests that there is a relationship between acute physical activity and cognitive performance, it is important to interpret these findings with caution given that the paradigms of the studies differ in several important domains, such as the type of exercise, the cognitive functions assessed, the age groups tested, as well as the physical and health condition of the participants.

The effect of physical exercise on cognitive and motor performance depends both on the intensity and the duration of the exercise (Etnier, Salazar et al. 1997; Tomporowski 2003; Kamijo, Nishihira et al. 2007). Various studies show that the effects of exercise on concentration, problem solving, reaction time, or discriminative ability follow an inverted-U curve (Tomporowski and Ellis 1985). First, intense but brief exercise does not appear to have much effect on brain functions (Hancock and McNaughton 1986; Tsorbatzoudis, Barkoukis et al. 1998) and prolonged but sub-maximal physical exercise leading to dehydration is associated with a reduction in cognitive performance. For example, a 2 h run on a treadmill at 65% of VO2max results in a significant disruption of short-term memory, psycho-motor abilities, and visual discrimination (Cian, Barraud et al. 2001). Physical exercise of moderate intensity and duration appears as the best to improve brain functions. Several studies show that beneficial effects on cognitive functioning (sensori-motor and cognitive performance) are reported for an exercise session producing a sub-maximal aerobic intensity (i.e., 20–80% of maximum heart rate) that is maintained for at least 15 mn (Clarkson-Smith and Hartley 1989; Hogervorst, Riedel et al. 1996). However, Gabbard and Barton (Gabbard and Barton 1979)

found an improvement on a test of mathematical skills only after 50 min of activity and not after 20, 30, or 40 mn.

The typical explanation for the facilitating effect of acute exercise on reaction time is an increase in physiological arousal and an enhanced amount of allocatable resources induced by the exercise (Gutin 1973; McMorris and Graydon 1997; Brisswalter, Collardeau et al. 2002; Kamijo, Nishihira et al. 2004). How the enhanced resources available during physical exercise are allocated to a concomitant cognitive task is less clear and seems to be moderated by cognitive effort and expertise (e.g., (Tomporowski 2003)). On the one hand, according to Sanders' (1998) (Sanders 1998) cognitive–energetic model, cognitive effort modulates arousal and activation which, in turn, are responsible for the resource allocation. On the other hand, cognitive expertise seems to facilitate the exploitation of the allocatable resources. With regard to visual attentional allocation, sub-maximal physical exercise seems both to generally enhance the speed of visual attentional performance and to specifically reduce the time needed to zoom attention (Pesce, Capranica et al. 2003).

The influence of physical exercise on the brain's neurochemistry and oxygen concentration has often been proposed to explain the improvement in sensory and cognitive performance associated with acute bouts of physical activity. For example, an increase in serotonin (associated with vigilance and sleepiness), dopamine and norepinephrine (associated with attention) was found after a short period of exercise in rats and in humans (Romanowski and Grabiec 1974; Elam, Svensson et al. 1987; Bailey, Davis et al. 1993; Vaynman and Gomez-Pinilla 2005; Querido and Sheel 2007). Another study has also shown a good correlation between levels of catecholamine concentrations induced by submaximal exercise and mental performance (Peyrin, Pequignot et al. 1987).

Finally and interestingly for our study, the exercise–attention relation also seems to be sensitive to age (Pesce, Cereatti et al. 2007).

To date, only few studies have evaluated the influence of exercise on performance decline induced by sleep deprivation. Most of these studies have examined exercise as an additional stressor. In these studies, participants have been found to be more alert immediately following exercise. Even exercises of short duration may help to fight sleepiness and fatigue due to sleep deprivation, i.e. an increase in beta power of human EEG (waking activity) has

been found immediately after a session of aerobic exercise (Youngstedt, Dishman et al. 1993; Oda, Matsumoto et al. 1999). In addition to the decrease in sleepiness, energy in the beta frequency band has been shown to reflect a cortical activation related to information processing and top-down attention processing. Exercise may reverse the impaired performance due to sleep loss, i.e. tasks involving short-term memory, complex addition and auditory vigilance (Horne and Porter 1975). On the other hand, Matsumoto et al. (Matsumoto, Mishima et al. 2002) suggested that exercise during an extended period of wakefulness lasting more than 24 hours results in an increased risk of human error.

It appears that the effects of exercise on cognitive and motor performance whilst exposed to sleep deprivation are still unclear. One aim of the present study will be to investigate whether physical exercise may be used as a countermeasure to sleepiness at the wheel induced by sleep deprivation.

5- Blue light (potential countermeasure)

The rods and cones of the outer retina are the photoreceptors responsible for the transduction of light information to the endogenous biological clock. These classical photoreceptors are sensitive to monochromatic green light (wavelength 550 nm). Currently it is demonstrated that another retinal system is involved in circadian photoreception: intrinsically photosensitive retinal ganglion cells (ipRGCs) containing photopigment the melanopsin (Berson, Dunn et al. 2002) (figure 2).

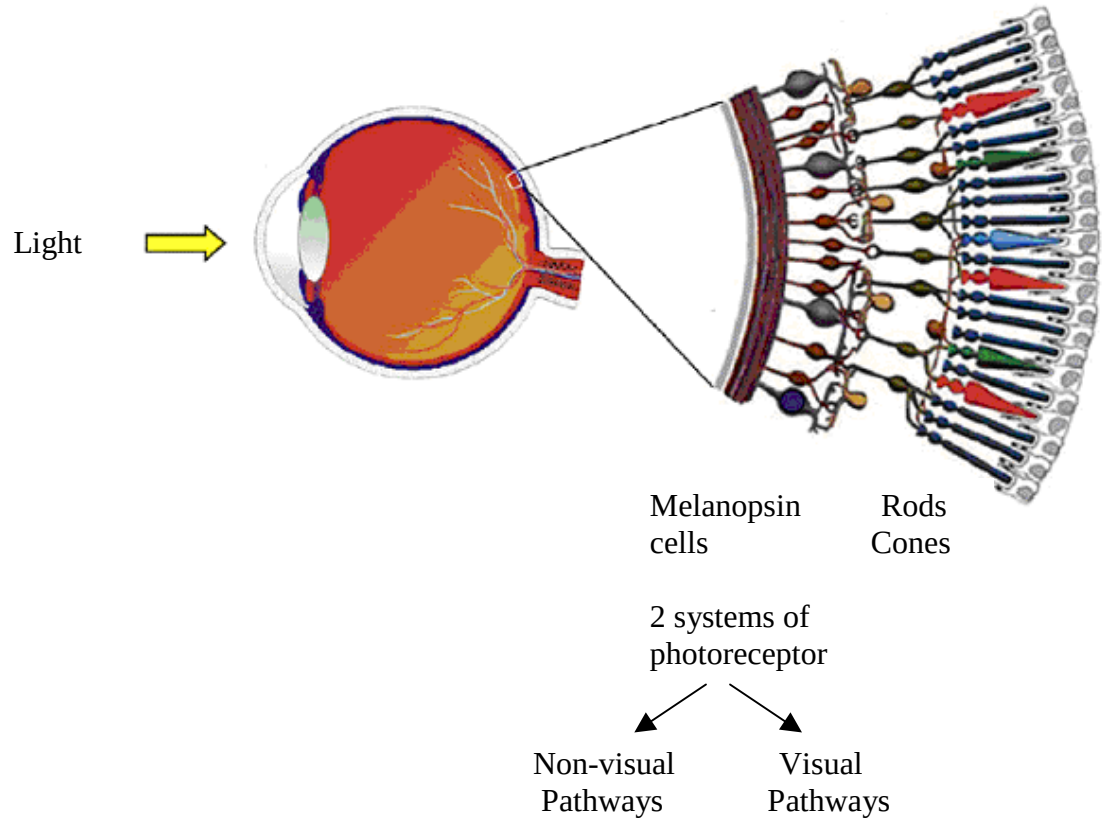

Figure 2: Diagram of the eye (in section) with a larger representation of the retina (right). The cones enable vision in low light, rods allow color vision. Both types of cells are the visual pathway. The melanopsin in the ganglion cells is involved in regulating biological rhythms. They are not the visual pathway and they project to structures involved in regulating the circadian system.

Intrinsically photosensitive retinal ganglion cells project (Gooley, Lu et al. 2003) to the suprachiasmatic nucleus (circadian clock), to the ventrolateral preoptic nucleus (sleep/wake regulation), to the ventral subparaventricular zone (sleep and activity regulation) and to the pretectal area (pupillary reflex) (Figure 3 (Berson 2003)). The light from these non-visual ways directly stimulates the brain structures involved in the control of vigilance, sleep, cognitive and psychomotor performance. These melanopsin photopigments are sensitive to monochromatic blue light (wavelength 460 to 480 nm) (Brainard, Hanifin et al. 2001).

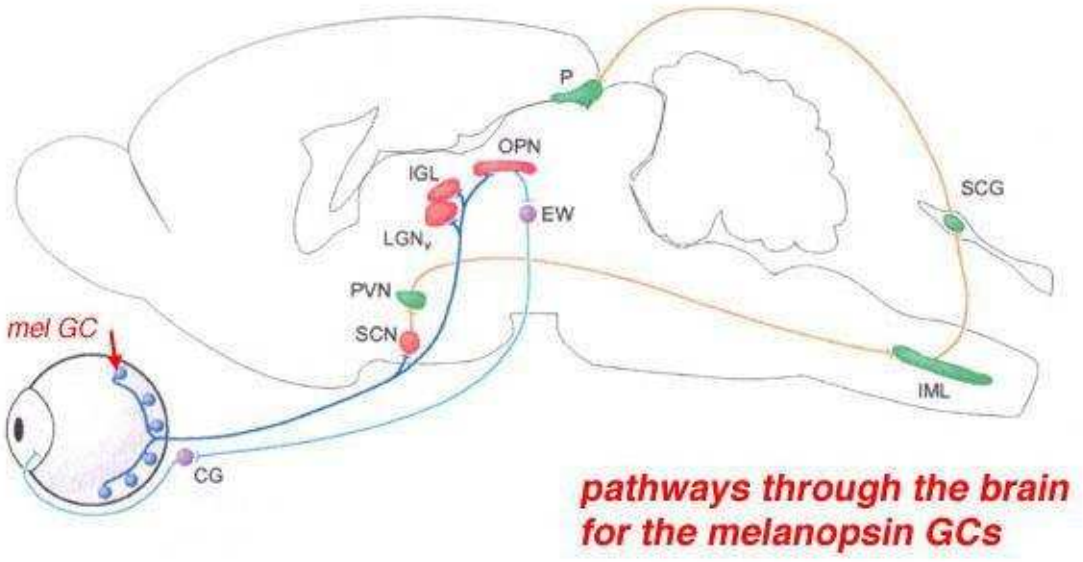

Figure 3

Diagram of the pathways taken by melanopsin ganglion cells to the brain. The pathway is to the suprachiasmatic nucleus (SCN) via the retinohypothalamic tract (blue) and on to the pituitary to regulate melatonin release. This circuit drives the circadian oscillator. A second pathway is through the lateral geniculate nucleus to the olivary pretectal nucleus (OPN) and to the Edinger Westaphal nucleus (EW) for control of the pupillary light reflex (light blue). After Berson, 2003.

Bright light exposure (polychromatic) at night has an acute alerting effect (improve performance, reduce attentional failures, suppression of theta-alpha activity of waking EEG) for review see (Cajochen 2007).

The work studying the effect of light blue or green has demonstrated the beneficial effect of higher nighttime exposure to blue light on endogenous circadian pacemaker reset (circadian phase shifting), pineal melatonin suppression, core body temperature, heart rate increase, subjective sleepiness decrease and improvement of vigilance (Campbell, Eastman et al. 1995). Recent studies indicate that very low intensity monochromatic light in the short-wave (460 nanometers, blue) range affects the human circadian timing system by inducing a phase shift similar to that of polychromatic light. Exposure to 2 hr of monochromatic light at 460 nm in the late evening induced a melatonin suppression concomitant with an alerting response and increased core body temperature and heart rate (Cajochen, Munch et al. 2005). Exposure to 460-nm monochromatic light for 6.5 hours during the biological night decreased subjective sleepiness, improved performance, decreased waking EEG power density in the

delta-theta frequency range, and increased the high-frequency alpha range (Lockley, Evans et al. 2006). Blue light widely participates in the functioning of the brain (Vandewalle, Maquet et al. 2009). In contrast, Figueiro et al. (Figueiro, Bierman et al. 2009) show that nighttime exposure to blue light improves objective alertness (EEG) but not performance. It could also have a beneficial effect on fatigue. Phipps-Nelson et al. (Phipps-Nelson, Redman et al. 2009) clearly confirm the beneficial effect of blue light on objective alertness but night-time exposure to blue light does not affect driving performance measured in the simulator.

Short wavelength light is a countermeasure of sleepiness and its very low intensity (5 photopic lux or 116 scotopic lux) can be used during nocturnal driving.

6- Technological countermeasures

The technological countermeasures that can be used to fight sleepiness at the wheel include on board or road equipments. To our knowledge, the rumble strips along the roads are the main technological countermeasures scientifically tested and whose results can be found in scientific publication. Indeed, the use of rumble strips to wake up drowsy drivers who inadvertently cross the line was tested and showed encouraging results (1993; 1997; 1997). Using a survey, the study of (Philips and Sagberg 2010) recently confirmed that the rumble strips help to reduce traffic accidents related to fatigue by waking drowsy drivers. In the future, this type of equipment should be standardized to prevent sleep-related accidents on highways or linear sections of monotone driving (ENTActionGroup15 2009). In the framework of the ENT group 15, a survey based on a questionnaire conducted among Norwegian drivers by TOI will determine the effect of rumble strips on sleepiness at the wheel.

In addition, a state of knowledge on the on-board equipments to fight sleepiness is done in the Yawn project.

Interindividual Differences

It is now well demonstrated that the nocturnal neurobehavioral performance vary considerably from one individual to another and the performance of only some subjects were significantly degraded during prolonged awakening (Leproult, Colecchia et al. 2003; Frey,

Badia et al. 2004; Philip, Taillard et al. 2004; Van Dongen, Baynard et al. 2004; Van Dongen, Maislin et al. 2004). Nocturnal performance of some subjects collapsed while they remain comparable to the level of arousal for others subjects. Previous studies have shown that individual differences in terms of characteristics of the circadian system, the duration and sleep architecture are not predictors of vulnerability to deprivation of sleep (Leproult, Colecchia et al. 2003; Van Dongen, Baynard et al. 2004; Taillard, Moore et al. 2006; Galliaud, Taillard et al. 2008). In contrast, it seems that some individual characteristics (such as age or cognitive profile) or certain biological markers of sleep pressure (adrenergic mechanisms, genetic polymorphisms and hormone levels of cortisol and amylase) would identify drivers vulnerable to sleep deprivation. We can also assume that the answers to counter-measurements depend upon the characteristics of each individual. This line of research is important because it will allow adapting prevention messages to the appropriate populations.

1- Age

Age is an important factor to consider because half of fatal and nonfatal accidents involving young people occur at night (Williams 1983). In a more controlled epidemiological study, young drivers had a dramatic increase in accident risk (Åkerstedt and Kecklund 2001).

Under controlled conditions, performance and subjective alertness were considerably more impaired in young than in older subjects (Frey, Badia et al. 2004; Philip, Taillard et al. 2004; Adam, Retey et al. 2006; Blatter, Graw et al. 2006; Duffy, Willson et al. 2009). The low degradation of performance during night in the elderly is associated with decreased amplitude of circadian rhythms with age (Blatter, Graw et al. 2006). Otmani et al. (2005) (Otmani, Roge et al. 2005) found in a simulator study that young professional drivers became sleepier than older subjects in terms of subjective ratings and EEG measures during early night driving.

2- Adrenergic mechanisms

Sleep deprivation impaired performance particularly in caffeine-sensitive subjects suggests that adrenergic mechanisms contribute to individual differences in waking-induced impairment of neurobehavioral performance (Retey, Adam et al. 2006). Subjective differences

in the psychostimulant effects of caffeine might reflect genetically determined differences in the adrenergic system (Alsene, Deckert et al. 2003). Distinct polymorphism of the adenosine A2A receptor gene (ADORA2A), which was associated with inter-individual sensitivity to caffeine effect on sleep and with inter-individual differences in anxiety symptoms after caffeine intake in healthy volunteers, is associated with inter-individual differences in EEG theta power increase (sleep pressure) during wakefulness (Retey, Adam et al. 2007). These findings provide direct evidence in humans that the adenosinergic system indeed modulates sleep and EEG correlates of sleep homeostasis, and show that a frequent polymorphism in the gene encoding adenosine contributes to high inter-individual variability in brain electrical activity during sleep and wakefulness (Landolt 2008). Adenosine promotes sleep, and the adenosine receptor antagonist (caffeine) promotes wake (Huang, Urade et al. 2007). Caffeine attenuates the EEG markers of sleep homeostasis during sleep as well as wakefulness (Landolt 2008).

Retey et al. (Retey, Adam et al. 2005) have shown that a functional polymorphism of the adenosine deaminase gene (ADA) is associated with inter-individual variability in sleep duration and slow wave sleep intensity as well as in EEG during wakefulness.

3- Genetic Polymorphism

Several studies indicate that the gene polymorphism PER3 (PERIOD3) affects the regulation of sleep and waking performance during prolonged wakefulness and that the COMT gene is involved in diurnal sleepiness. Membership Genetics may well determine individual vulnerability to sleep deprivation and be responsible for the deterioration in performance after sleep deprivation.

3.1- PER3 variable number tandem repeat (VNTR) polymorphism

The PER3 gene is involved in the circadian clock which generates biological rhythms. PER3 has a more robust circadian oscillation than the others clock genes. PER3 shows strong circadian rhythms in brain areas such as the suprachiasmatic nucleus (SCN) and the organum vasculosum lamina terminalis (OVLT) (Takumi, Taguchi et al. 1998) but also in many peripheral tissues. The phase of PER3 expression in leukocytes correlates with the phases of melatonin and cortisol, and with habitual sleep timing (Archer, Viola et al. 2008). Taken

together, these data show that the rhythm of PER3 expression in leukocytes represents a reliable molecular marker for the assessment of the entrained phase in healthy individuals.

The PER3 gene contains a variable number tandem repeat (VNTR) polymorphism, in which a 54-nucleotide coding-region segment is repeated 4 or 5 times. The Per3 polymorphism correlated significantly with extreme diurnal preference, the longer allele (PER 5/5) associating with morningness and the shorter allele (PER 4/4) with eveningness (Jones, Ellis et al. 2007). However, there was no difference in sleep wake schedules between the two groups and it was only in PER 5/5 individuals that the authors found correlations between PER3 rhythms and sleep-wake timing and melatonin and cortisol levels.

PER3 polymorphism is associated with specific EEG characteristics. PER3 5/5 individuals have much higher alpha activity in REM sleep, theta/alpha activity during wakefulness (marker of sleep pressure during wakefulness) and delta activity during NREM sleep (marker of sleep pressure during sleep) than PER4/4. Sleep pressure during wakefulness is higher in PER3 5/5 subjects. This higher sleep pressure during wakefulness and especially during prolonged wakefulness would affect performance.

Another study (Viola, Archer et al. 2007) has shown in a healthy population that PER3 polymorphism predicts individual differences in the sleep-loss-induced decrement in cognitive performance, and that this differential susceptibility may be mediated by its effects on sleep homeostasis (sleep latency, SWS, theta activity in the waking EEG). PER3 5/5 individuals showed impaired nocturnal performance compared to PER3 4/4 individuals. In PER3 5/5 individuals, the sleep pressure increased more during wakefulness and the amplitude of circadian rhythm of performance (more decrement of performance during extended wakefulness) was higher than in PER3 4/4 individuals. By contrast, the circadian rhythms of melatonin, cortisol and peripheral PER3 mRNA expression were not different. From fMRI-assessed brain responses to an executive task, after an extended wakefulness, the brain activity in frontal and temporal area decreased in PER3 5/5 individuals but not in PER3 4/4 individuals (Vandewalle, Maquet et al. 2009).

However, Goel et al (2009) (Goel, Banks et al. 2009) have demonstrated that the PER3 VNTR polymorphism is not associated with individual differences in neurobehavioral responses to chronic sleep deprivation, although it is related to one marker of sleep homoeostatic response during chronic sleep deprivation.

In conclusion, PER3 polymorphism affects sleep homeostasis but only slightly circadian regulation and could predict individual differences in the sleep-loss induced decrement in performance.

3.2- Polymorphism of the gene coding for the catechol-O-methyltansferase (COMT gene)

The COMT gene is present on the chromosome 22 at 22q11.2. The COMT polymorphism will be explored by the demonstration of a G to A substitution in codon 158 of this gene, by the restriction enzyme Nlalll. Concerning susceptibility to excessive daytime sleepiness, some studies have assessed the association between COMT genotype (catechol-O-methyltransferase is a key enzyme of the monoaminergic neurotransmission) involved in sleepiness and some neurological pathologies involved in diurnal excessive sleepiness (narcolepsy, Parkinson disease). A study (Dauvilliers, Neidhart et al. 2001) reported a sexual dimorphism and a strong effect of COMT genotype on narcolepsy severity. Female narcoleptics with high COMT activity fell asleep twice as fast as those with low COMT activity during the multiple sleep latency test (MSLT), while the opposite was true for men. COMT genotype also strongly affected the presence of sleep paralysis and the number of REM sleep onsets during the MSLT. This study reported the first genetic evidence for the critical involvement of the dopaminergic and/or noradrenergic systems in human narcolepsy. Moreover, a pilot study (Frauscher, Hogl et al. 2004) has shown that COMT activity contributes to daytime sleepiness in patients with Parkinson disease owing to its involvement in the metabolism of dopamine. An ESS score greater than 10 was 4 times more frequent in patients carrying the COMT low-activity allele (LL or LH genotypes) than in those with the HH genotype.

4- Hormonal

Hormonal dosage may also make it possible to determine hormonal phenotypes (vulnerable/resistant to sleepiness and responder/non-responder to countermeasures). Salivary concentration of amylase is highly associated with sleep homeostatic pressure. Seugnet et al (2006) (Seugnet, Boero et al. 2006) have demonstrated that 28 h of waking increased amylase activity and mRNA levels and can be considered as a marker for sleep drive. Another study (Spiegel, Leproult et al. 1999) has shown that chronic sleep debt has a harmful impact on carbohydrate metabolism and endocrine function. It is known that chronic sleep deprivation

modifies cortisol secretion (stress hormone) in humans with attenuation of the daytime rhythm and increase during the nocturnal period.

Thus, several studies indicate that the gene polymorphism PER3 (PERIOD3) affects the regulation of sleep and the waking performance and that the COMT gene is involved in sleepiness. Genetics belonging may well determine individual vulnerability to sleep deprivation and be responsible for the deterioration in performance after sleep deprivation.

5- Baseline individual cognitive pattern

The effects of sleep deprivation on cognitive performance have been extensively studied and show a range of cognitive impairment as a reduction in vigilance, working memory and executive functions (Walker 2008). There are large intra and inter individual differences in this impairments, explaining a substantial proportion of the variability of sleep deprivation effects (Van Dongen, Rogers et al. 2003).

Studies have indeed shown that, for a given cognitive task, performance degradation due to sleep deprivation is variable among individuals (inter-individual differences). A significant decrease in speed and accuracy of cognitive performance was observed for some individuals while others performed the task as effectively as when they were not sleep-deprived (Frey, Badia et al. 2004). These results demonstrated individual differences in sensitivity to sleep deprivation. Some individuals are therefore likely to be more affected than others by sleep debt. This sensitivity can be considered as a stable dimension or, as proposed by Van Dongen et al. (2004), a trait-like differential vulnerability (Van Dongen, Baynard et al. 2004). Indeed, the decreased performance observed during a night of sleep deprivation is highly reproducible for a given individual between different sessions of sleep deprivation (Leproult, Colecchia et al. 2003).

It has also been shown that the degree of impairment resulting from sleep deprivation depends on which cognitive tests are performed. Thus, different cognitive tasks may be affected to varying degrees for a given individual (intra-individual differences). Individuals with the most degraded performance on one aspect of cognitive functioning are not necessarily those who have the most impaired performance on another aspect of this functioning (Frey, Badia et al. 2004; Van Dongen, Baynard et al. 2004). Each individual therefore has an individual impairment profile in response to sleep deprivation.

According to Van Dongen et al. (2004), the basis of differential sleep deprivation vulnerability and of the individual impairment profile may be explained by the cognitive performance of individuals when they are not sleep-deprived. These authors suggest that the variability in responses to sleep deprivation is dominated by variability of baseline performance of these cognitive tasks. Individual differences observed in cognitive performance in situations of sleep deprivation could thus at least partly be explained by individual differences in the baseline pattern of cognitive performance.

These results suggest that effective countermeasures to sleepiness induced by sleep deprivation may vary depending on the baseline cognitive pattern of individuals. This hypothesis seems supported by the results of Killgore et al. (Killgore, Kahn-Greene et al. 2009). They have shown that caffeine improved performance of sleep-deprived individuals for cognitive tasks requiring inhibitory control and ability to focus on the completion of multiple subgoals. These authors hypothesize a possible contribution in their results of individual differences in the baseline cognitive pattern.

Our goal will be to determine whether the individual cognitive pattern contributes to differential sleep deprivation vulnerability and induces individual differences in the effectiveness of countermeasures.

Realized experiments

The effects of blue light versus coffee and placebo on night-time highway driving: a study of inter-individual differences (France)

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Our 24/7 society induces behavioural reduction of daily sleep duration and extensive periods of wakefulness or activities in the circadian deep (3-5 a.m.) which are causes of sleepiness-related accidents (Akerstedt, Philip et al. 2011), especially traffic accidents. Owing to conflicts between physiological needs and social or (Lockley, Evans et al. 2006) professional activities, countermeasures to fight this sleepiness need to be developed. To date, caffeine and naps have been shown to be effective in real-life driving studies (Philip, Taillard et al. 2006; Sagaspe, Taillard et al. 2007) but they have some limitations (differences between individuals in terms of efficiency, limited efficiency duration, side-effects). As caffeine and naps are self-administered countermeasures that involve stopping the car at rest stops, many sleepy drivers (46 %) continue to drive (Anund, Kecklund et al. 2008). Reasons for not stopping include being far from any possible rest stops, being relatively close to one's destination, or lack of insight into one's state of alertness 5. When drivers do not stop driving, they use in-car countermeasures (e.g. opening window or turning on the radio) (Anund, Kecklund et al. 2008) which are inefficient (Reyner and Horne 1998; Schwarz, Ingre et al. in press). The development and evaluation of in-car countermeasures is a major public health issue for the prevention sleepiness-related accidents.

We conducted a study to compare the effects of continuous exposure to monochromatic light in the short wavelengths (blue light, 468 nm), placed in the middle of the dashboard, with coffee (2*200 mg of caffeine) or caffeine placebo on 4h night-time driving performance in healthy male volunteers. Intrinsically photosensitive retinal ganglion cells that contain melanopsin photopigment known to respond directly to light with a peak spectral sensitivity in the short-wavelength range (460-480 nm blue-light) (Berson, Dunn et al. 2002) projects to the suprachiasmatic nucleus (master biological clock) and to the brain area involved in the regulation of arousal (Gooley, Lu et al. 2003) by a specific non-visual tract. Continuous exposure to blue light has proved effective on subjective and objective correlates of alertness and performance in the evening (Chellappa, Steiner et al. 2011) and at night (Cajochen, Munch et al. 2005; Lockley, Evans et al. 2006). This type of continuous exposure at levels as low as 20 lux could be used as often as required during night-driving as a preventive countermeasure to sleepiness at the wheel and to reduce the risk of accidents in sleepy drivers.

Study objectives

Primary objective
To compare the effects of continuous blue light exposure during driving with those of coffee (2*200 mg of caffeine) and coffee placebo on 4h night-time driving performance in young (20-25 years) and middle-aged (40-50 years) healthy volunteers.

Secondary objectives
To determine the effect of age in the effectiveness of countermeasures (blue light and coffee)

To determine individual differences (cognitive, genetic and hormonal) in the impairment of neurobehavioral functions from sleep loss and in the effectiveness of countermeasures (blue light and coffee).

To determine the effects of blue light on quality and quantity of sleep after night-time driving in young and middle-aged healthy volunteers.

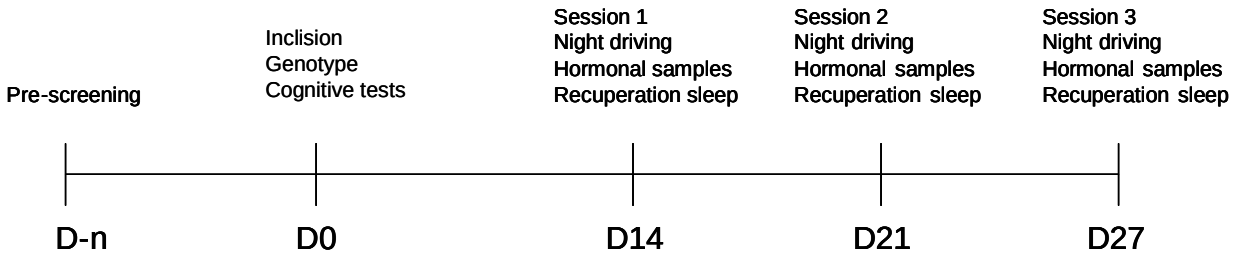
Experimental design

This was an interventional study: Open label, Randomized, Crossover, Comparative versus referent countermeasure of sleepiness: coffee (2*200 mg of caffeine) and placebo.

The study was divided into the following periods:

1. **selection period** without treatment between selection and inclusion visits to check the absence of exclusion criteria with questionnaires, polygraphic recording (respiratory sleep disorders and periodic leg movements) and actimetry (sleep efficiency, Total sleep time)

2. **acute treatment period**, each volunteer was randomly allocated to receive either continuous blue light exposure or 2*200 mg of caffeine or placebo of caffeine during night driving with at least 1 week between treatment.



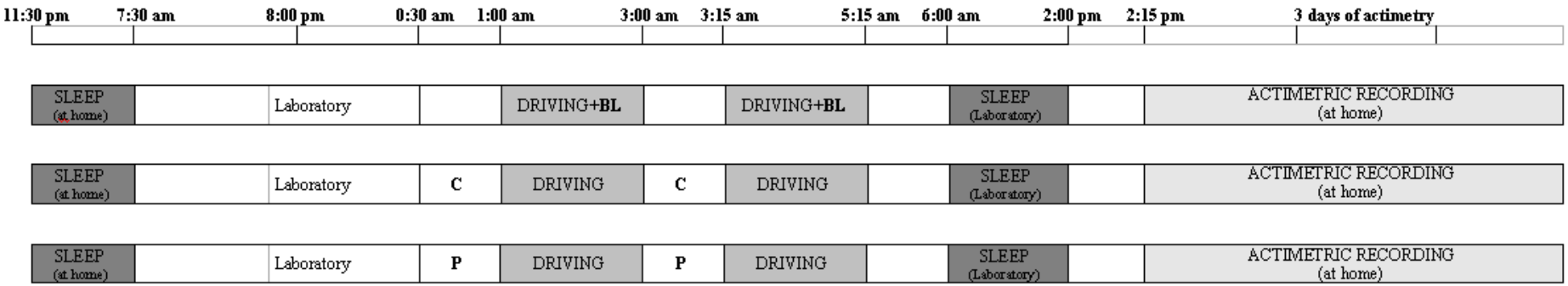


Figure 1. Design of the protocol representing sleep-driving period for the three substance conditions (placebo, coffee and blue light).

Selection of participants

Inclusion criteria

- Healthy volunteers
- Caucasian
- Aged between 20-25 years or 40-50 years
- Male
- BMI <25
- Moderate caffeine drinkers (2-3 cups by day)
- Non professional drivers had had their driving license for at least 2 years and drove between 10000 and 20000 km per year
- Showing a morning or evening chronotype (Horne questionnaire score >58 or < 42 for young subjects and Horne questionnaire score >6 4 or < 53 for middle-aged subjects)

The patient's informed consent was obtained at the inclusion.

Exclusion criteria

- Evidence of psychopathology (self-reports symptom inventory SCL-90R score >59 on the general symptomatic index and the following symptom dimensions: depression, anxiety, paranoid ideation and psychoticism)
- Evidence of sleep disorders (Items of Basic Nordic Sleep Questionnaire >3),
- Evidence of excessive daytime sleepiness (Epworth sleepiness scale score >9)
- Hypopnea-apnea index > 5 (assessed by polygraphy)
- Periodic leg movement index > 14 (assessed by polygraphy)
- Sleep efficiency < 85 % (assessed by actimetry during 7 consecutive days)
- Alcohol consumption and consumption of any medication or illicit drugs (urinary tests),
- Smokers
- Shift-workers and jet-lag the month before their inclusion in the study
- Severe controlled or uncontrolled diseases (psychiatric disorders, neurological disorders, sleep disorders, hepatic or renal failure, unstabilized diabetes, neoplasic disorders, cardiovascular disorders, pulmonary disorders, digestive disorders,…)

Treatment

Blue light

Blue light (goLITE BLU®, Philips, NL) was LED light sources with a spectral wavelength of 468 nm ± 8 nm and an intensity of 225μw/cm2). The light source (14 x 14 x 2.5 cm) was placed in the middle of the dashboard at approximately a 25° horizontal angle of gaze and approximately 75cm from the participant's eyes. The light device was used according to the manufacturer's recommendations in order to increase safety and avoid blue light hazard. Luminance at the eye level was in order of 20 lux.

Figure 1: Photography of the car, showing placement of the LED light source panel.

Coffee

Each participant drank 125 ml of coffee (about half a cup of coffee, containing 200 mg of caffeine) or 125 ml of placebo (containing 15 mg of caffeine) 30 minutes before the nighttime driving session and after 2 hours of driving.

Coffee and placebo was prepared from single packs of the relevant instant coffee (normal or decaffeinated) provided by Nestlé. Coffee contained 4.25% caffeine and placebo (decaffeinated coffee) contained less than 0.3% caffeine. Placebo and coffee was not distinguishable by taste or appearance.

Criteria of assessment

Primary efficacy criterion

- Number of inappropriate line crossings (ILC) identified from the video recordings.

Secondary efficacy criteria

- Standard deviation of the position of the car
- Self-rated sleepiness during driving
- Timing, quantity and quality of 3 subsequent sleeps

Secondary criteria

- Chronotype
- Caffeine sensitivity
- PER3 polymorphism
- COMT polymorphism
- ADORA2A polymorphism
- Saliva cortisol concentration before and after the driving session and the after sleep recuperation

Clinical assessment methods

EFFICACY

Driving session

The night-time driving session started at 1:00 AM and finished at 5:15 AM. All participants drove 400 km (250 miles) on the same 2-lane motorway for all conditions. After 2 hours of driving (200km, 125 miles), subjects took a 15-minute break. Driving conditions were a straight motorway on weekdays with usually light traffic conditions and in fair weather. Subjects were instructed to maintain a constant speed (130 kph; 80 mph), to drive in the center of the lane, and not to cross the painted lines separating the lanes, except to overtake a slower vehicle. During the whole experiment, a professional driving instructor monitored the driving speed and was ready to take control of the car (equipped with dual controls) if needed. No verbal communication was allowed between the drivers and co-pilots unless a specific instruction had to be given. Saliva will be collected before and after the driving session and after sleep recuperation.

The main driving ability criterion was the number of inappropriate line crossings (ILC). This measure was selected because epidemiologic findings have shown that 65% of sleep-related accidents occur after an ILC. Several studies have also shown that impaired daytime alertness induces lateral deviations during driving and that sleep-related accidents frequently occur with a single car driving off the road and hitting an obstacle with no reaction from the driver. We have also demonstrated that the number of ILCs is affected by sleep deprivation and improved by classic countermeasures to sleep loss. ILC was identified by a Continental Automotiv® video system, which measures and registers the lateral position (cm) of the car (10 times/sec) from the right lateral lane marker of the road. The Continental Automotiv® video system was calibrated according to the lane characteristics. An ILC was recorded when the car crossed a right or left lateral lane marker, whatever the duration and the amplitude of the crossing. Exceptions were overtaking manoeuvres or some other necessary driving action. All ILC were confirmed manually by video-recording analysis. The scorer of video recordings was blind to the driving condition. Lateral Position was defined as being 0 when the car was in the center of the lane, with positive value to the right and negative values to the left. Standard deviation of the position of the car (cm), derived of lateral position, indicates weaving of the car, used as another parameter to identify driving performance.

Subjective sleepiness

Participants was asked to rate their sleepiness on the Karolinska Sleepiness Scale (a 9-point scale from 1 = “extremely alert” to 9 = “very sleepy, great effort to keep alert, fighting sleep”).

Polysomnography

Three electroencephalograms (F3/A2, C3/A2, O1/A1), 1 electromyogram, 2 electrooculograms, and 1 electrocardiogram was recorded during the night after driving.
Signals was digitized at a sampling rate of 256 Hz and filtered with a digital filter at a cutoff frequency of 35 Hz.
Data was manually analyzed by an experienced sleep technician in 30-second epochs according to Rechtschaffen and Kales' recommendations (Rechtschaffen and Kales 1968). Non-rapid eye movement (NREM) sleep (stages 2, 3, and 4) during sleep was retained for spectral analysis.

Timing, quantity and quality of 3 subsequent sleeps
Sleep duration, quality and timing were determined by actigraphy (Actiwatch®, Cambridge Neurotechnology, UK). This device monitors body movements and allows calculation of nocturnal sleep episodes and nocturnal awakenings. Time in bed was also computed as the time difference between going to bed in the evening and getting up in the morning. Sleep efficiency was calculated as the ratio of time asleep to time in bed expressed as a percentage.

SUBJECTS TYPING

Genomic (PER3, COMT, ADA, ADORA2A) DNA
Genomic DNA was extracted from 2*5ml blood sample (tube with EDTA solution).

Saliva cortisol
Saliva was directly collected from mouth to tube. Samples were stored at -18°c before analysis. Saliva cortisol concentrations were determined by RIA.

Caffeine sensitivity assessment
Subjects reporting nocturnal sleep disturbances after caffeine intake in the afternoon were considered as caffeine sensitive and subjects reporting no problems sleeping after caffeine in the afternoon were considered as caffeine insensible.

Cognitive tests : Evaluation of attentional components
- *Tonic and phasic Alertness*: The examination includes a simple and a cued reaction time task with a visual test stimulus and an acoustic cue. The difference between simple and cued reaction time is a measure of phasic alertness. (Computerized test)
- *Vigilance and sustained attention*: There are four tasks with different stimuli (3 unimodal tasks: 1 acoustic, 2 visual; one bimodal task: visuo-acoustic) that assess sustained attention or vigilance. Each task can be run with high (sustained attention) or low event rate (vigilance) of critical stimuli. (Computerized test).
- *Divided attention*. A dual task is used. The visual task consists of crosses that appear in a random configuration in a 4 x 4 matrix. The subject has to detect whether the crosses form the corners of a square. The acoustical task includes a regular sequence of high and low beeps. The subject has to detect an irregularity in the sequence. (Computerized test).
- Selective attention (Zazzo's cancellation task, short 8-line version). This test measures the ability to cross out as fast and as exactly as possible target signs among distracters on a sheet of white paper containing 8 lines of signs. In our study, we considered the time spent to complete all 4 lines and the omission errors and false alarms. (Pen-paper test)

Cognitive test : Evaluation of executive functions
Inhibition

- Go/No-Go: this test requires a subject to emit a simple motor response (Go) to one cue while inhibiting the response in the presence of another cue (No Go). There are twice more Go signals than No-Go signals. Reaction time and percentage of error will be measured.
- Incompatibility : during incompatibility task , the tendency of interferences will be tested by a SR incompatibility. Subjects were instructed to squeeze as fast as possible in response to a left- or right-pointing arrow presented on a computer screen. The arrow determined whether the response was to be compatible (e.g., right arrow with right hand squeeze) or incompatible (right arrow with left hand squeeze). Reaction time and percentage of error will be measured in the two conditions.

Cognitive speed
- The Trail Making Test (TMT) is used to assess cognitive speed, visual motor tracking, divided attention, and mental flexibility. It consists of two parts. In Part A, the patient has to connect numbers from 1 to 25 in the correct order as fast as possible (cognitive speed and visual motor tracking). (Pen and paper test). The score was total duration in seconds and the number of correct moves.
- The Digit Symbol subset of the WAIS-R is used to measure coding ability. This test is a performance measure which requires the subject to code nine simple symbols matched with nine numerals. The subject is given 90 seconds to code all items on the test. (Pen and paper test)

Flexibility
- TMT-B : numbers from 1 to 13 and letters from A to M must be connected in alternating fashion, beginning at 1-A and ending at M-13. Total score is given by time spent to complete each part (Pen and paper test)
- TEA Flexibility : Two stimuli (letter and digit) are displayed at a time. Subjects will be instructed to push on right or left key in according to the target. (Computerized test)

Working Memory
Updating memory task. Subjects must recall digit number list.

SELECTION

<u>Actigraphy</u>
Actimeters were used to quantify our volunteers' sleep duration and quality. This device monitors body movements and allows calculation of mean nocturnal sleep episodes and of nocturnal awakenings. Time in bed was also computed as the time difference between going to bed in the evening and getting up in the morning. Sleep efficiency was calculated as the ratio of time asleep to the time in bed, in percentage. To rule out any sleep-wake schedule disorders each subject was monitored for 7 days before being included in the study. Subjects were included if they have a mean sleep efficiency of at least 85% during the 7 days of recordings.

<u>Polygraphy</u>
A nocturnal polygraphy (nasal flow, oxygen saturation, two respiratory effort belts, snore, position, leg movement) was performed to eliminate subjects suffering from sleep disorders. Subjects presenting a AHI > 5 or a PLM index >14 was excluded of study.

<u>Habitual sleep patterns</u>

The evaluation of usual sleep schedules, sleep quality, sleep needs and sleep hygiene was assessed by the Basic Nordic sleep questionnaire. This 22-items questionnaire evaluate the quality of sleep over the previous 3 months as measured by a frequency scale ranging from 0 (never or less than once a month) to 5 (almost everyday or everyday) (Partinen and Gislason 1995).

Chronotype assessment

The chronotype was assessed by Horne and Ostberg questionnaire (Horne and Ostberg 1976). This questionnaire contains 19 items about individual rising and bedtimes preferred time of physical and mental performances and alertness after rising and before going to bed. It mainly use 4-choices items.

Sleepiness

Chronic daytime sleepiness was assessed by the Epworth Sleepiness Scale which rates the tendency to fall asleep in 8 different situations in daily life.

Self-reports symptom inventory SCL-90R

The evidence of psychopathology was assessed by the Symptom Checklist 90 (SCL-90). This questionnaire is a psychiatric self-report inventory. The 90 items in the questionnaire are scored on a five-point Likert scale, indicating the rate of occurrence of the symptom during the time reference. It is intended to measure symptom intensity on nine different subscales. It has been shown to have a good reliability as its internal consistency is high.

Statistical considerations

Determination of sample size

The sample size calculation (G power software) was done in order to allow demonstrating a slight difference between the 2 countermeasures (coffee and blue light) with a power of 90 % and a type-I error =5% approximately 48 subjects have to be included in the study:

Effect size f = 0.3
$\alpha_{\text{err prob}} = 0.05$
Power $(1-\beta_{\text{err prob}}) = 0.9$

Total sample size: 48 **(24 young and 24 middle-age)**

Statistical Analysis

Results are presented as mean ± standard error (SE).
Driving performance and actimetric recordings were analyzed by mixed-model analysis using a composed symmetry structure to adjust for serial correlation across time.
For driving performances, the predictive factors were mean lateral position, mean cumulative number of ILC and mean standard deviation of the position of the car, while the fixed effects were age (young vs. middle-age), substance (placebo vs. coffee vs. blue light), and driving session (first vs. second). For actimetric recordings, the predictive factors were sleep efficiency, total sleep time and bedtime recorded after the driving sessions, while the fixed effects were age (young vs. middle-age), substance (placebo vs. coffee vs. blue light), and day (first vs. second vs. third). The subject was considered as a random intercept assumed to be

constant across conditions. The fully saturated model was run and the final mixed model included all main effects and interaction terms. Fisher's LSD post-hoc comparisons were used when a significant difference was found. The SPSS® statistical package (Version 18; Chicago, USA) was used for all analyses.

Results

Eight data out of 288 were not included in the analysis. They concerned 5 drivers who did not manage to finish one or various second night-time driving sessions because they were too sleepy to drive. Three incomplete driving sessions were under placebo, 2 under coffee and 3 under continuous blue light exposure.

As some participants complained about dazzle during continuous blue light exposure and as the variability of driving performance (ILC) was high for this driving condition [Standard error (SE) for Blue light = 6.15, for Placebo = 5.12 and for Coffee = 2.72)], a hierarchic classification based on the Ward method was used to check whether all participants performed equally. The result showed that 8 participants exhibited a significantly higher number of ILC (102.38 ± 13.22) than the others (14.58 ± 2.22). Results from these 8 participants (3 young and 5 middle-aged) were thus removed. The other participants declared that blue light had no incidence on their visual comfort.

Driving performance

Mean lateral position

Mean lateral position of the car was 23.00 cm ± 1.65 (toward the right) with placebo, and closer to center of the lane with coffee and continuous blue light exposure (19.55 ± 1.40, P=0.004 and 20.94 ± 1.50, P=0.004 respectively).

Inappropriate line crossings

Both countermeasures improved the driving performance as the number of ILC was lower with coffee (12.51 ± 2.08, P=0.001) and continuous blue light exposure (14.58 ± 2.18, P=0.003) than with placebo (26.42 ± 3.86) (Figure 2). A significant effect of the moment of driving was also found, indicating a higher number of ILC during the 2nd night-time driving session (21.32 ± 2.64) than during the 1st night-time driving session (14.59 ± 2.07, P=0.001). No significant effect of age, chronotype or caffeine sensibility was found and no significant interaction were found.

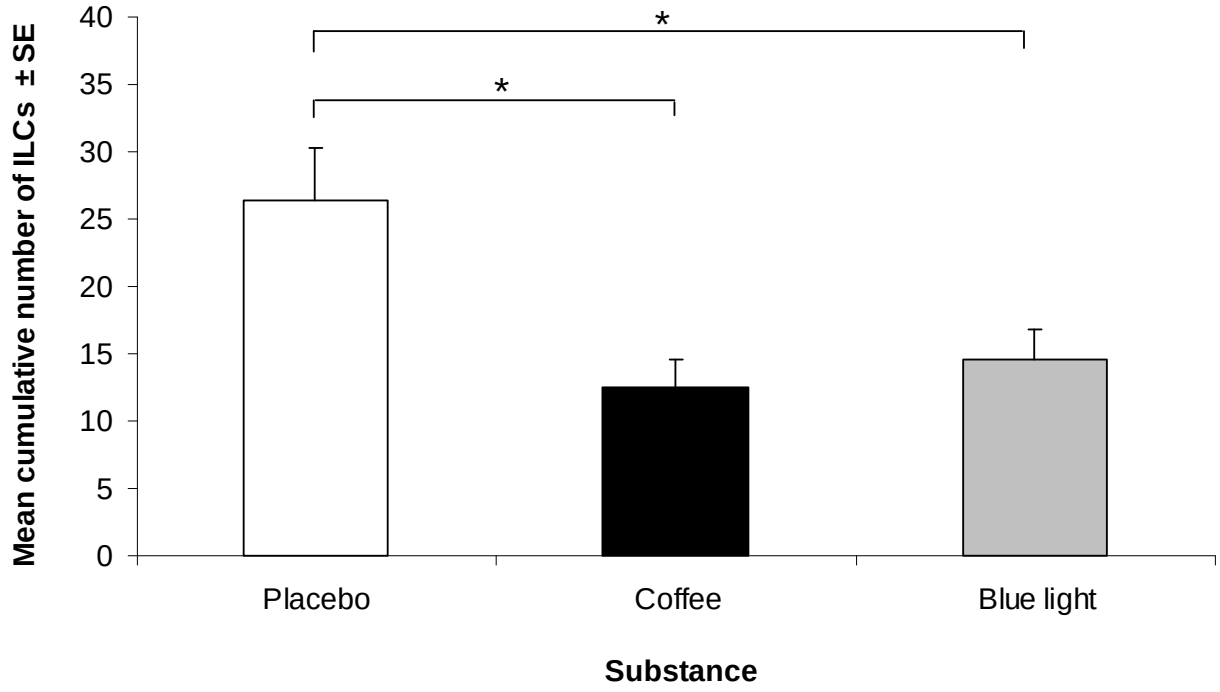


Figure 2. Mean cumulative number of inappropriate line crossings in all substance conditions
* P< 0.01

Weaving

Countermeasures and driving session had significant effects on the mean standard deviation of the position. Indeed, the deviation was smaller with coffee (24.74 ± 0.6, P=0.001) than with placebo (28.56 ± 0.91) and tended to be smaller with continuous blue light exposure (26.87 ± 0.74, P=0.051). Moreover, a greater deviation was found during the second night-time driving session (25.53 ± 0.53) than during the first one (27.99 ± 0.73, p=0.001). No significant effect of age, chronotype or caffeine sensibility was found and no significant interaction was found.

Self-perception of sleepiness

Sleepiness measured by Karolinska Scale scores was influenced by age ($F(1, 54.44)=7.79$; $p<0.01$) as mature evaluated themselves more alert (5.94 ± 0.22) than young subjects (6.83 ± 0.15, p=0.007). There was also a significant increase in sleepiness with the driving session ($F(1, 168.87) = 36.85$; $p<0.001$)), indicating a higher score during the 2nd night-time driving session (6.96 ± 0.17) than during the 1st one (5.85 ± 0.19, p=0.001). Finally, a significant interaction of substance with driving session was found ($F(2, 168.87)=5.76$; $p<0.005$, Figure 3): during 1st night-time driving session, participants evaluated themselves more alert with blue light than with placebo (p=0.010) whereas during 2nd night-time driving session, participants evaluated themselves more alert with placebo than with coffee and blue light (respectively, p=0.027 and p=0.010).

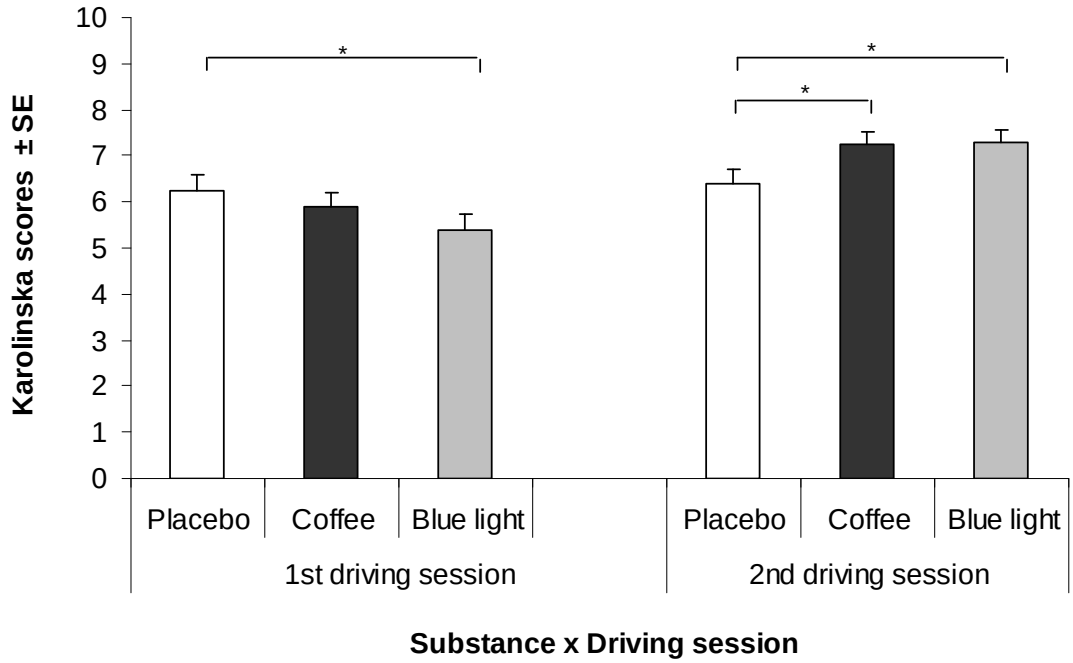


Figure 3. Sleepiness measured by Karolinska scores in all substance and driving session conditions

Timing, quantity and quality of 3 subsequent sleeps

Sleep efficiency

The results indicated a significant effect of Age on sleep efficiency. Indeed, middle-aged subjects had higher sleep efficiency (89.36 ± 0.89) than young subjects (85.24 ± 0.86, $P<0.001$). No effect of Substance was found.

Total sleep time

There was a significant effect of Day on Total Sleep Time, indicating a longer sleep time on the first day (455.85 ± 9.62) than on the third (421.62 ± 9.85, $P=0.01$) or second ones (389.90 ± 9.64, $P=0.001$). No effect of Substance was found.

Bedtime

Bedtime was influenced by Age and Day. Middle-aged subjects went to bed earlier (11.44 pm ± 7 min) than young subjects (1.25 am ± 12 min, $P<0.001$). Participants went to bed earlier on the first day (0.16 am ± 12 min) than on the second (0.56 am ± 13 min, $P=0.006$). No effect of Substance was found.

Genomic DNA and cortisol dosages

The dosages (Genomic (PER3, COMT, ADA, ADORA2A) DNA and cortisol saliva) are in progress

Baseline individual cognitive pattern

If the individual cognitive profile contributes to driving performances in sleep deprived drivers and leads to individual differences in the effectiveness of countermeasures to sleep deprivation, we expect to observe positive associations between cognitive performances and driving performances in the three conditions of countermeasure.

Correlations between cognitive performances and the position on the road are summarized in Tables 2, 3 and 4 and correlations between cognitive performances and inappropriate line crossings in Tables 5, 6 and 7, and this for the three driving conditions. Only significant correlations are presented.

For the placebo condition, the standard deviation of the vehicle position on the road is associated with one cognitive test at T1 (Set Test) and 6 tests at T2 (Stroop, Isaacs set Test, phasic alert, Incompatibility and flexibility). The number of inappropriate line crossings is associated with 3 cognitive performances at T1 (divided attention, vigilance and incompatibility) and 8 at T2 (TMT, Isaacs set test, alert, divided attention, Incompatibility, flexibility, working memory and vigilance).
For the caffeine condition, the standard deviation of the vehicle position is associated with one cognitive test at T1 (Set Test) and 3 tests at T2 (Codes, Isaacs Set test and divided attention). The number of inappropriate line crossings is associated with cognitive performances in 2 tests at T1 (Zazzo cancellation test and Isaacs set test) and one test at T2 (Stroop).
For the blue light condition, the standard deviation of the vehicle position is associated with 2 cognitive tests at T1 (divided attention and vigilance) and 2 tests at T2 (Stroop and Isaacs Set Test). The number of inappropriate line crossings is associated with cognitive performances in 2 tests at T1 (Zazzo cancellation test and Isaacs set test) and 3 tests at T2 (divided attention, flexibility and Vigilance).

Thus, we observe that many cognitive variables were associated with driving performances, reinforcing the hypothesis of a link between cognitive performances and the impact of sleep deprivation on driving skills.

In the placebo condition, these associations were more numerous. These results suggest that the use of sleepiness countermeasures could result in a reduction of individual differences due to cognitive performances.

Moreover, the increase of the number of associations between cognitive tests and driving indicators between T1 and T2, especially in the placebo condition, seems to reveal an increase in vulnerability with an increase of sleep deprivation for individuals with the lowest cognitive performances.

The number of cognitive variables is nevertheless too large to provide a clear interpretation of these results. More complex analysis (principal component analysis, hierarchical analysis,…) will be perform. They will allow to identify which cognitive components (latent variables) are the most associated with driving performances in situations of sleep deprivation. They will also allow outlining individual cognitive profiles which could be put in relation with driving performances, taking into account the countermeasures used and the duration of driving time.

		T1	T2
Placebo	**Zazzo cancelation test**	X	X
	Codes	X	X
	TMT	X	X
	STROOP	X	Nb correct responses in the interference condition (tau(44)=-0,242, p=.03)
	Isaac Set Test	Nb uncorrected errors (tau(47)=0,247, p=.03)	Nb uncorrected errors (tau(44)=0,298, p=.01)
	Alert	X	RT in the condition with warning signal (r(44)=0,315, p=.03)
	Divided Attention	X	X
	Incompatibility	X	RT in the compatible condition (r(44)=0,360, p=.017) RT in the incompatible condition (r(44)= 0,379, p=.011)
	Flexibility	X	RT for the letter task in the single task condition (r(44) = 0,316, p=.036) TR for the number task in the single task condition (r(44) = 0,379, p=.011)
	Working memory	X	X
	Vigilance	X	X

Table 2 : Significant correlations between the standard deviation of the position and performances on cognitive tests at T1 and T2 for the placebo condition

		T1	T2
Caffeine	**Zazzo Cancelation Test**	X	X
	Codes	X	Nb errors (r(45)=0,257, p=.031)
	TMT	X	X
	Stroop	X	X
	Isaac Set Test	Nb correct responses at 15" (r(47)=0,422, p=.003) Nb correct responses at a 30" (r(47)=0,382, p=.008) Nb uncorrected errors (tau=0,323, p=.005)	Nb uncorrected errors (tau(45)=0,274, p=.018)
	Alert	X	X
	Divided Attention	X	Standard deviation of RT for the visual task in dual-task condition (r(45)= 0,321, p=.0,032)
	Incompatibility	X	X
	Flexibility	X	X
	Working Memory	X	X
	Vigilance	X	X

Table 3 : Significant correlations between the standard deviation of the position and performances on cognitive tests at T1 and T2 for the caffeine condition

		T1	T2
Blue light	**Zazzo Cancelation Test**	X	X
	Codes	X	X
	TMT	X	X
	Stroop	X	Nb correct responses interference task (tau(45)=-0,274, p=.017)
	Isaac Set Test	Nb responses with doubt (tau(48)=0,232, p=.047)	Nb of correct responses at 30" (r(45)=0,335, p=.024) Nb uncorrected errors(tau(45)=0,272, p=.019) Nb responses with doubt (tau(45)=0,262, p=.029)
	Alert	X	X
	Divided Attention	Standard deviation RT visual task in single task condition(r(48)=0,293, p=.043)	X
	Incompatibility	Mean RT pour la condition incompatible (r(48)=0,363, p=.011)	X
	Flexibility	X	X
	Working Memory	X	X
	Vigilance	X	X

Table 4 : Significant correlations between the standard deviation of the position and performances on cognitive tests at T1 and T2 for the blue light condition

		T1	T2
Placebo	**Zazzo Concelation Test**	X	X
	Codes	X	X
	TMT	X	TR atTMT A (r(44)=0,306, p=.044)
	Stroop	X	X
	Isaac Set Test	X	Nb uncorrected errors (tau(44)=0,238, p=.045)
	Alert	X	RT in the condition without a warning signal (r(44)= 0,411, p=.006) RT in the condition with a warning signal (r(44)=0,485, p=.001) Standard deviation of RT in the condition with a warning signal (r(44)=0,427, p=.004)
	Divided Attention	Standard deviation of RT for the visual task in the single task condition (r(47)=0,490, p=.000) RT for the auditive task in the single task condition (r(47)=0,413, p=.004)	RT for the visual task in the single task condition (r(44)=0,490, p=.001) Standard deviation of RT for the visual task in the single task condition (r(44)=0,362, p=.016) RT for the auditive task in the single task condition (r(44)=0,385, p=.010)
	Incompatibility	RT in the incompatible condition (r(47)= 0,312, p=.033)	RT in the compatible condition (r(44)=0,420, p=.005) RT in the incompatible condition (r(44)=0,459, p=.002)
	Flexibility	X	RT for the letter task in the single task condition (r(44)=0,473, p=.001) RT for the number task in the single task condition (r(44)=0,498, p=.001) RT for the number task in the switching condition (r(44)= 0,314, p=.038)
	Working Memory	X	RT (r(44)=0,368, p=.014)
	Vigilance	Nb of missing responses for the first 15 minutes (Tau(47)=0,248, p=.032) Nb of missing responses for the last 15 minutes (Tau(47)=0,324, p=.004)	Nb of missing responses for the first 15 minutes (Tau(44)=0,292, p=.012) Nb of missing responses for the last 15 minutes (Tau(44)=0,292, p=.012)

Table 5 : Significant correlations between the number of inappropriate line crossings and performances on cognitive tests at T1 and T2 for the placebo condition

		T1	T2
Caffeine	**Zazzo Cancelation Test**	Nb of correct responses in 4 lines (tau(47)=0,260, p=.032)	X
	Codes	X	X
	TMT	X	X
	Stroop	X	Nb correct responses in the interference condition (tau(45)=-0,232, p=.047)
	Isaac Set Test	Nb correct responses at 15" (r(47)=0,291, p=.047)	X
	Alert	X	X
	Divided Attention	X	X
	Incompatibility	X	X
	Flexibility	X	X
	Working Memory	X	X
	Vigilance	X	X

Table 6 : Significant correlations between the number of inappropriate line crossings and performances on cognitive tests at T1 and T2 for the caffeine condition

		T1	T2
Blue Light	**Zazzo Cancelation Test**	X	X
	Codes	X	X
	TMT	X	X
	Stroop	X	X
	Isaac Set Test	X	X
	Alert	X	X
	Divided Attention	Nb errors for the auditive task in the single task condition (Tau(48)=0,260, p=.033) Standard deviation of RT for the visual task in the single task condition(r(48)=0,539, p=.000)	Standard deviation of RT for the visual task in the single task condition (r(45)= 0,335, p=.025)
	Incompatibility	X	X
	Flexibility	X	RT for the number task in the single task condition (r(45)=0,388, p=.008) Standard deviation of RT for the number task in the single task condition (r(45)=0,407, p=.006)
	Working Memory	X	X
	Vigilance	Nb of missing responses for the last 15 minutes (Tau(48)=0,269, p=.017)	Standard deviation of TR for the last 15 minutes (r(45)=0,303, p=.043)

Table 7 : Significant correlations between the number of inappropriate line crossings and performances on cognitive tests at T1 and T2 for the blue light condition

Discussion

The main findings of this randomized controlled study were that continuous blue light exposure during nocturnal driving resulted in significantly reduced ILC and weaving compared with caffeine placebo, and that it was similar to caffeine (a countermeasure reference) in improving driving ability. Both countermeasures caused a driving closer to the center of the road. Continuous nocturnal blue light exposure was effective in short and long driving periods and throughout the night, even at the circadian trough. The alerting effect of blue light exposure was observed in both young and middle-aged drivers, even if age-related changes are known to reduce light transmission, particularly that of blue light (Turner and Mainster 2008). Chellappa has demonstrated that humans homozygous for the PER3 5/5 allele are particularly sensitive to blue-enriched light, so continuous blue light exposure during nocturnal driving could be proposed in first intention to these specific drivers (Chellappa, Viola et al. 2011).
Recently, we demonstrated the gradual standard deviation of lateral position increment during prolonged nocturnal motorway driving (Sagaspe, Taillard et al. 2008) and its relationship with alcohol-induced impairment (Verster, Taillard et al. 2011). Nocturnal driving impairment under placebo corresponds to a blood alcohol concentration (BAC) close to 0.10%. Nocturnal driving impairment under continuous blue light exposure and caffeine intake corresponds to a blood alcohol concentration (BAC) inferior to 0.08% as well as caffeine intake improves driving performance (below the legal limits of United Kingdom and some US states).

Our results are consistent with those of a previous randomized trial of blue light or blue-enriched light on alertness and cognitive performance. That study demonstrated that nocturnal exposure to blue light was effective in enhancing cognitive performance on a sustained attention task (Cajochen, Munch et al. 2005; Lockley, Evans et al. 2006; Viola, James et al. 2008; Phipps-Nelson, Redman et al. 2009; Chellappa, Viola et al. 2011), but not on higher executive functions tasks (Chellappa, Steiner et al. 2011). In contrast with our results, blue-light exposure was not reported to increase driving simulator performance (Phipps-Nelson, Redman et al. 2009). This inconsistency may be due to the lower intensity blue light used in the previous study (1 lux, 2uw/cm2).
Using a sustained attention task, various studies showed a better tolerance to sleep deprivation with aging (Philip, Taillard et al. 2004; Adam, Retey et al. 2006; Duffy, Willson et al. 2009). Blatter showed that young and old adults exhibited similar sustained attention decrements during the night (Blatter, Graw et al. 2006). The present study confirms our previous finding that nocturnal driving impairment is not affected by age (Sagaspe, Taillard et al. 2007).
On the one hand, occasional continuous nocturnal blue light exposure has no residual effect on quantity and timing of subsequent sleep. On the other hand, 17% of drivers experienced eye-related discomfort and/or visual problems. This discomfort greatly impaired the ability to maintain a stable lane position. Drivers should be informed about this side-effect and blue light-intolerant drivers should not use blue light as a countermeasure to fight nocturnal sleepiness. The complaints about dazzle made by some subjects could be due to the high irradiance level used in our study. The irradiance level commonly used in studies demonstrating the beneficial effect of blue light on nocturnal alertness is lower (Cajochen, Munch et al. 2005; Lockley, Evans et al. 2006). To increase tolerance, we suggest testing low irradiance and/or better placement of the light source panel in the car (e.g. above the driver's head) on nocturnal driving performance. Even if the light device used in this study has been tested for ocular safety (Anderson, Glod et al. 2009), the potential risks of retinal damage due to blue light hazard (Algvere, Marshall et al. 2006) should not be forgotten particularly with regard to long-term use.

At this stage of the analysis, we did not bring to determine individual differences in the impairment of driving performance from sleep loss and in the effectiveness of countermeasures to fight nocturnal sleepiness.

A limitation of our study is that it was conducted only on men owing to the effects of menstrual cycle phase on cognitive performance during sleep deprivation (Wright and Badia 1999). Future studies are needed to investigate the effect in sleep-deprived women. Furthermore, this study tested the effect of occasional continuous nocturnal blue light exposure. Future studies should investigate the effect of continuous nocturnal blue light exposure used repeatedly.

Provided it does not dazzle drivers, continuous nocturnal blue light exposure could be used as an in-car countermeasure to fight nocturnal sleepiness at the wheel in both young and middle-aged drivers. Used occasionally, it does not affect subsequent sleep.

Exercise versus caffeine on simulated driving performances (France – MCT)

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Introduction

The risk of traffic accidents increased considerably during any night-time activity when the circadian rhythmicity and the duration of the wakefulness combine together to affect cognition. Like reaction time, many psychomotor performances degrade after 16 hours of wakefulness, they dropped at sunshine and have their lowest values after the peak of melatonin secretion (Cajochen, Khalsa et al. 1999). During the nocturnal phase of the circadian rhythm, the drowsiness is drastically increased, as well as the risk of accidents due to human error (Akerstedt, Kecklund et al. 2001). In terms of road safety, the drowsiness would be responsible for approximately 30% of traffic accidents (NTSB 1995). However, it is not possible to prohibit night driving and different counter-measures have been proposed. The best known are to stop the vehicle to have a nap or to drink coffee or other waking substances. An alternative to stimulate the vigilance could be the use of physical activity (for review, (Tomporowski 2003)). If visual alertness processes are taken as an example, it has been shown that physical activity both increase the speed of execution and reduce the reaction time. These effects would be dependent on the age (Pesce, Cereatti et al. 2007). The literature on sleep deprivation also indicates that the vigilance is improved at the end a physical exercises. The beta activity recorded on the EEG (awakening activity) information and alertness processes are increased just after an aerobic exercise. However to our knowledge, no study have been done to know if exercise can be used as countermeasure to driving sleepiness during sleep deprivation. Our hypothesis is that nocturnal driving performances on a simulator could be improved by an exercise of moderate intensity. Driving simulators are good tools to record driving performances while both the environment and exercise can be controlled.

Participants

Determination of the size of the sample
The size of the sample (G power software), to determine a light difference between both countermeasures (caffeine and physical activity) with a 90 % power and an error of type(chap) 1 = 5 24 subjects must be included in this study:
F = 0.50 Effect size; _ err prob = 0.05; Power (1-_ err prob) = 0.9
Size of the esteemed sample: 24 (12 mature and 12 young people)

Inclusions
Table 1 presents the mean and Standard deviation obtained on the 24 participants dispatched in the 2 groups (young: 22,4+3,2 years and mature: 45,4+2,8 years). To be included in the study, they have to be free of sleep troubles (checked by polygraphic recordings), to sleep about 8 hours by night (checked by actimetry) and to be of “intermediar” chronotype (Horne

and Ostberg's questionnaire), they also have to have a driving licence and drive at least 10 000 km a year. They all had a triangular test to evaluate their maximal aerobic power (MAP) by the use of a cyclo-ergometer.

Table 1 : Average and standard deviation of the main variables of the groups of participants. No significant difference are shown between the 2 groups with the exception of the age, of the past of driving and of the km/year.

	Jeunes		**Matures**	
Participants	mean	*ET*	mean	*ET*
Age (années)	21,3	*1,5*	44,1*	*2,8*
Taille (cm)	180,7	*5,1*	179,7	*7,9*
Weight (kg)	71,0	*9,2*	77,1	*11,2*
BMI	21,7	*2,1*	23,8	*1,9*
SCL 90 R GSI	42,0	*5,3*	44,8	*5,6*
SCL 90 R Anx	42,0	*3,6*	44,0	*5,4*
SCL 90 R Dep	44,3	*5,7*	44,3	*6,9*
SCL 90 R Psy	45,5	*3,5*	45,5	*3,5*
SCL 90 R Par	45,3	*5,5*	43,6	*5,0*
H & O	50,3	*3,5*	58,7	*6,0*
BNSQ	0,1	*0,3*	0,1	*0,3*
ESS	5,5	*3,0*	6,9	*2,7*
Sleep efficiency	88,2	*4,7*	86,5	*3,3*
Driving licence since (years)	3,0	*1,6*	24,3*	*5,5*
Km/years	14666,7	*4811,6*	27083,3*	*13048,6*
Coffee/days	1,3	*0,6*	2,2	*1,2*
VO2 max	47,5	*5,6*	42,0	*7,1*
PMA	291,3	*42,6*	285,0	*44,0*
50% PMA	145,6	*21,3*	142,5	*22,0*

Protocol

The subjects carried an actimeter during the 3 days and nights which preceded the 3 experimental sessions.
For each of these experimental session, participant arrived at the laboratory at 8 pm. After a standard meal, he wait for the tests with quiet activities (reading, game of strategy) (figure 1).

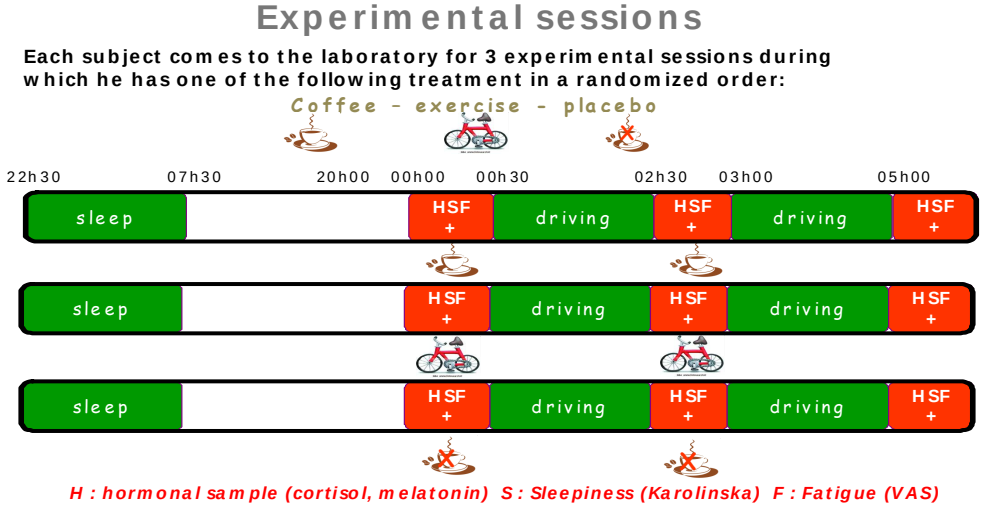

Figure 1 : Experimental protocol describing the succession of the recordings made for each participant in the experiment.

Methods

The driving performances were recorded on a driving simulator during 2x2 hours at 00:30 am and at 03:00 am after:

- A cup of coffee (caffeine 2*200 mg),
- A cup of caffeine free coffee (placebo),
- 20 min of physical activity, 5 min of warming-up, followed by 15 min in a constant intensity set at 50 % of the PMA of each participant.

The driving simulator (INRETS SIM2), was developed with VIGISIM ANR-05-PDIT-005-01 (Davenne, Lericollais et al. 2012). It simulate a very monotonous highway (the visual environment of the section of A62 Langon-Agen-Langon), without other car in circulation, nor event which may stimulated the alertness and make interference. Every selected participant took part in about 2 hours individual sessions of familiarization to get use with the equipment. The criteria used to quote the driving performances are the number of inappropriate line crossings (ILC) and the standard deviation of the position of the vehicle in the lane (LD).

Subjective sleepiness before and after the session of driving either by VAS, or by the Karolinska Sleepiness Scale (KSS), anxiety and fatigue by VAS were made at 00:25 am, 02:35 am, 2:55 am and at 05:05 am.

The participants' sleep was recorded after each experimental session by actimetry.

Statistical analyses have been made by negative binomial regression, by ANOVA with one, two, three ways and by ANOVA with repeated measures rANOVA.

Results

Driving performances

For the "placebo" condition, the rANOVA with 2 factors (group (young - mature) x driving hours (the 1st - 2nd - 3rd and 4th hour) shows that there is no significant difference for the driving performances (ILC and DL) between the young and mature participants (figure 2). But there is an effect of the hour of driving and the post-hoc test of Scheffé, shows that the performances degrade gradually with the driving duration. The performances obtained during the 2nd hour and the 3rd hour, i.e. before and after the break are the same which indicates that this break of half an hour between 02:30 am and 03:00 am do not restore the driving performances. The analysis of the slopes of regression curves obtained between the 1st and the last hour of the experimental sessions shows that the driving performances of the "young" degrade faster than the of the "mature" participants. The risk factor for the "young" to drive between 04:00 am and 05:00 am after 3 hours of driving is estimated at twice the one of the "mature" participants (3,57 versus 2,07, $p > 0,05$).

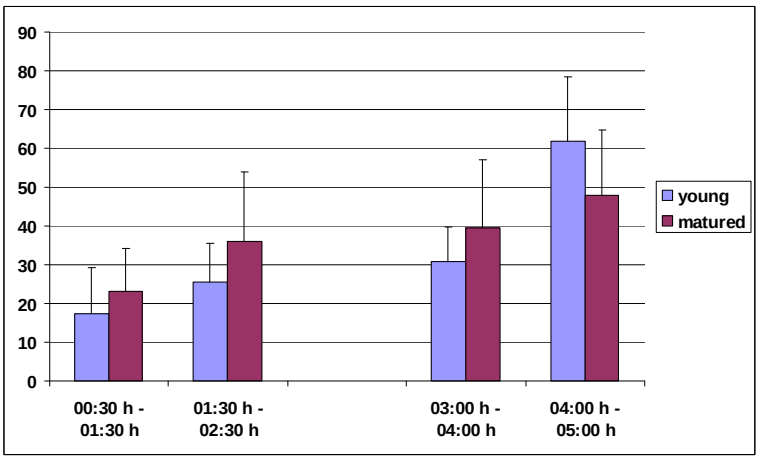

Figure 2 : Number of line crossing (LC) and standard deviation of the position of the vehicle in the lane (LD) observed for the "young" and "mature" participants during the 4 hours of driving.

The comparison of the results obtained in the "placebo" and "coffee" (rANOVA) for each groups shows that the caffeine is significantly very effective to improve the driving performances for both "young" and "mature" participants (figure 3 and 4). But, caffeine is significantly effective only during the 2nd and the 3rd hour of driving in young participants. Coffee taken during the break at 02:30 am is very efficient for 2 groups as shown by driving performances which remain significantly improved during the 2 following hours. A cumulative effect with the first cup of coffee taken 2 hours before might explain these results.

However, the comparison of the results obtained in the conditions "placebo" and "exercise" (rANOVA) for each group shows that the exercise has a significant effect but in opposite ways: for the "young" participants, exercise degrades the driving performances which follow the 2 sessions of 20 min of exercise while for "mature" participants, these performances are significantly increased, but only after the 1st exercise. Exercise during the break has no effect on the 2 following hours.
The comparison of the results obtained in the conditions "placebo" and "exercise" (rANOVA) for each group shows that the effects of "exercise" are significantly less effective than "coffee" to improve the driving performances.

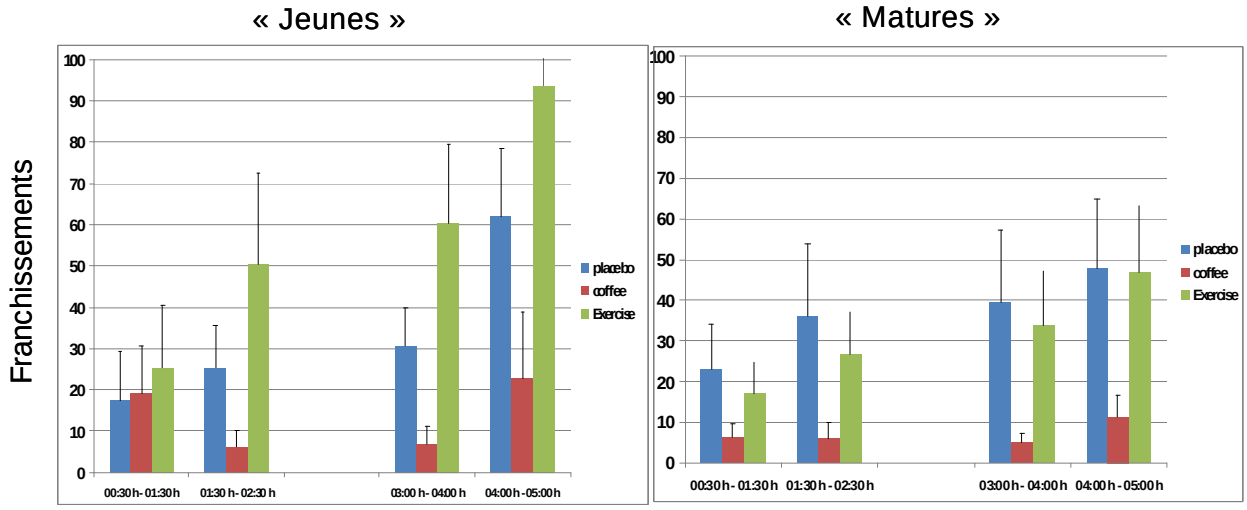

Figure 3: Number of inappropriate line crossings (ILC), for the "young" and "mature" participants in the 3 driving conditions (placebo, coffee, exercise).

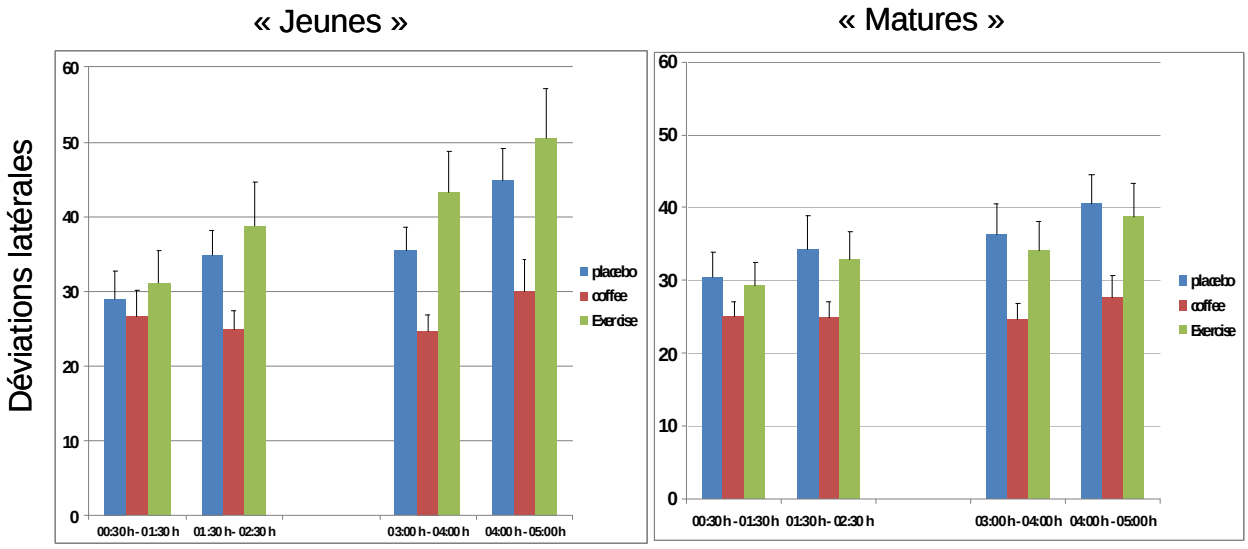

Figure 4: Standard deviation of the position of the vehicle in the lane (LD), for the "young" and "mature" participants in the 3 driving conditions (placebo, coffee, exercise).

Subjective somnolence and Fatigue

Subjective sleepiness estimated by the KSS (figure 5), is the same in the "young" and "mature" participants, but depends on driving conditions. The participants are always sleepier at the end of driving. The break has a positive effect on subjective sleepiness.

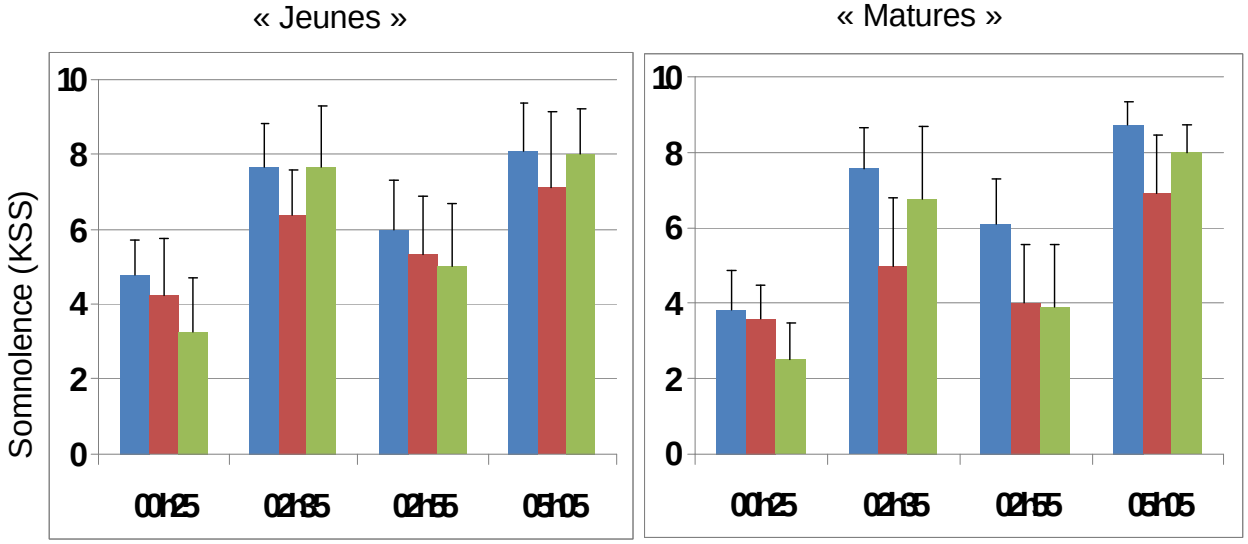

Figure 5: Subjective sleepiness estimated by the KSS for the "young " and " mature" participants in the 3 driving conditions (placebo, coffee, exercise).

Similar results are found for the subjective fatigue (figure 6).

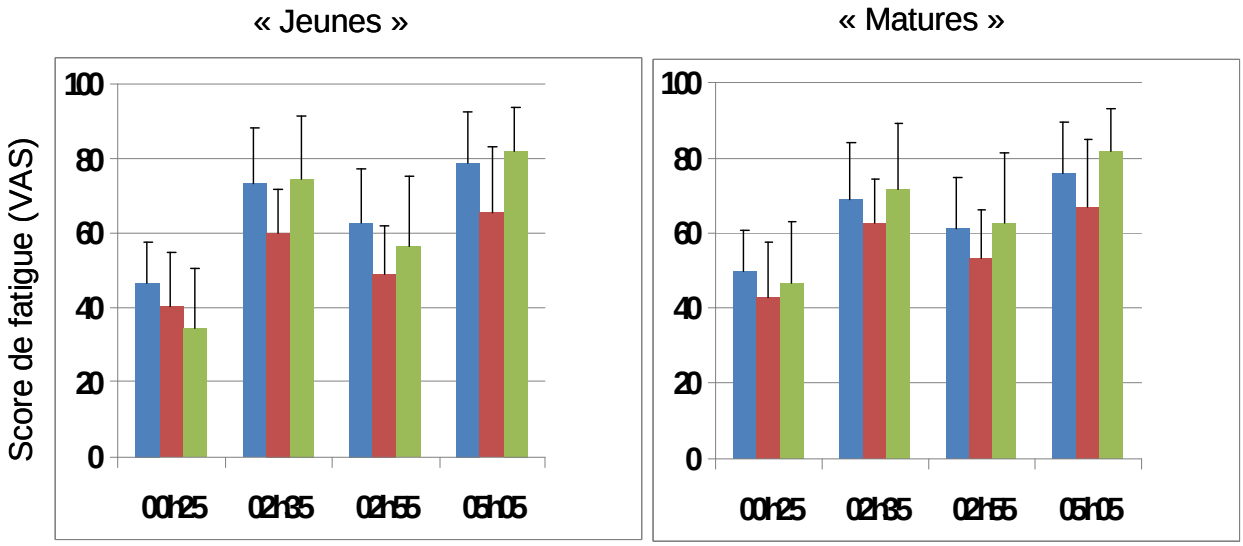

Figure 6: Subjective fatigue estimated by the VAS for the "young " and " mature" participants in the 3 driving conditions (placebo, coffee, exercise).

Sleep after the experimental sessions

ANOVA shows that the length and efficiency of the sleep after the experimental sessions are increased for the "young", but unchanged for the “mature” participants. The effects observed are not dependent on driving conditions.

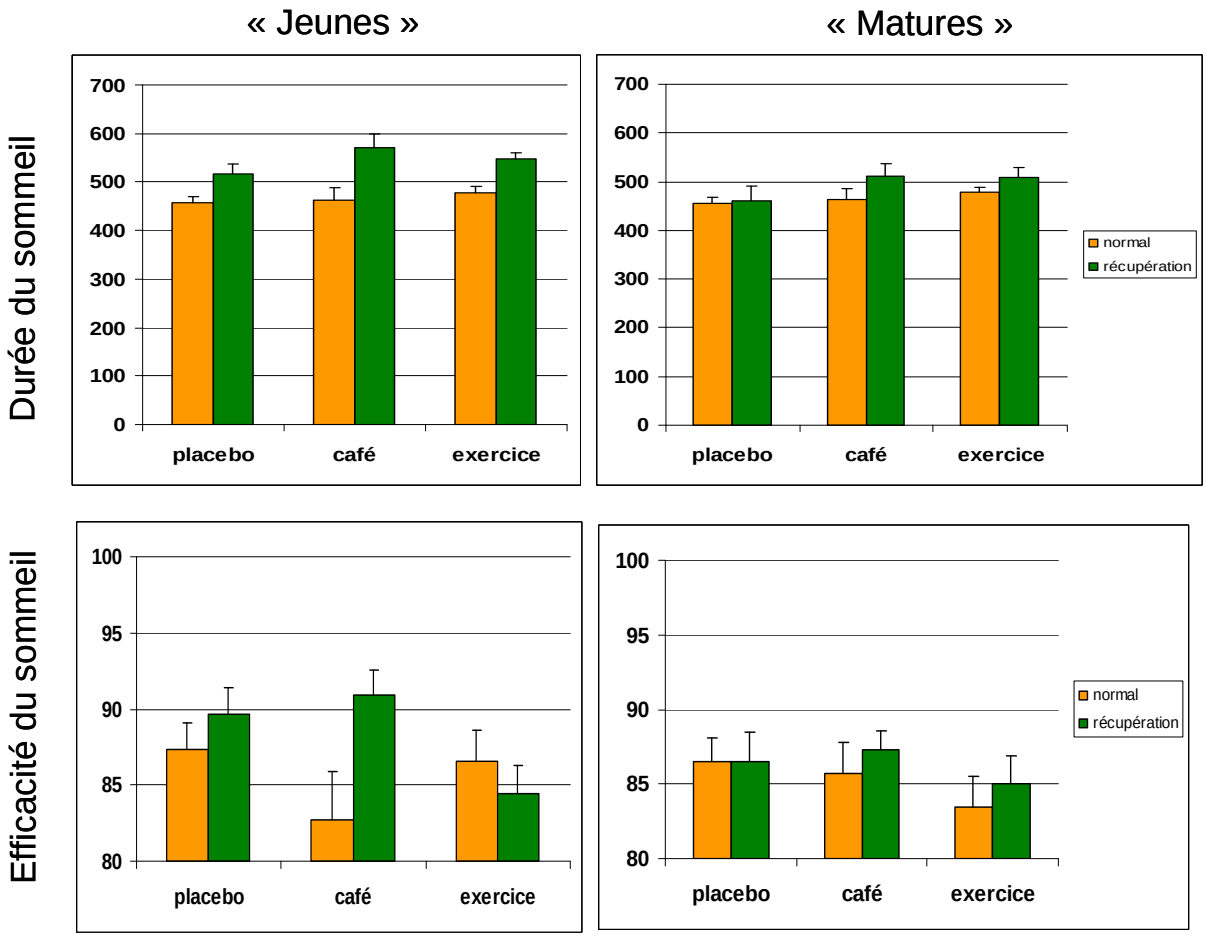

Figure 7: Duration and efficiency of the sleep recorded after each experimental session, for the "young" and "mature" participants, in the 3 driving conditions (placebo, coffee, exercise).

Hormonal dosages

Takings were done to measure the rates of cortisol and melatonin (figure 1) and frozen at -18°C. The dosages are not made yet.

Conclusions

This innovative study produced some rather unexpected results. The subjects "young people" are more affected by the night-driving than are the older one. With regard to the later, their performances degrade with both time-of-night and duration of driving. The break with placebo in the middle of the 4 hours of driving has an effect on the subjective perception of fatigue and sleepiness, but does not improve the performances of driving.

Caffeine is very effective for all participants with, however, an effect more restricted for the "young people". It does not seem to change the sleep taken during the morning following the session of tests.

Exercise slightly improves the driving performances of the "mature" participants. On the contrary exercise, as it was proposed, has deleterious effects effect for the "young" participants. These results might indicate that exercise during the night has an effect on alertness dependent on the age (Blok and de Looze 2011). However, the absence of works on the effects of exercise on vigilance or other cognitive process during the night-phase of the circadian rhythm brings us to have other hypothesis. For example, exercise would not be effective during the night because the man is not scheduled by the central clock to be active at night. To test it, the same protocol could be done at various time-of-day. Another hypothesis would be that the power of the exercise (50% of the VMA) was to strong for young people (Brummer, Schneider et al. 2011). What means that the level of exercise should be modulated according to the age of the participants to have optimal effects on the driving performances.

Publications from these studies

Acts of congress

TAILLARD J., CAPELLI A., SAGASPE P., LEGER D., ELBAZ M., PHILIP P. L'exposition continue à la lumière bleue améliore aussi bien qu'une prise de caféine l'aptitude à la conduite automobile nocturne : Etude randomisée contrôlée en situation réelle. *Congrès du Somme*il, Strasbourg, 24-26 novembre 2011.

TAILLARD J., CAPELLI A., SAGASPE P., ANUND A., AKERSTEDT T., PHILIP P. Continuous nocturnal blue light exposure improves the ability to drive at night as well as caffeine intake: a randomized controlled study in real driving condition. *SLEEP 2012 26th Annual Meeting of the Associated Professional Sleep Societies*, June 9 –13, 2012,

TAILLARD J, Effects of blue light and physical activity on the nocturnal driving performance., Congrès de la mi-parcours du Predit 4 : le carrefour de la recherche et de l'innovation dans les transports terrestres, 10- 12 mai 2011, Bordeaux

DAVENNE D, LERICOLLAIS R., DENISE P., GAUTHIER A., Effets de l'activité physique sur la vigilance en milieu de nuit, *14ème Congrès de l'ACAPS*, Rennes, 24-26octobre 2011

DAVENNE D, LERICOLLAIS R., GAUTHIER A., Exercise as a countermeasure to sleepiness during the night, 16th annual Congress of the ECSS, Liverpool, july 6-9th, 2011

DAVENNE D, The effects of exercise versus coffee on nighttime performances on a driving simulator, Congrès de la mi-parcours du Predit 4 : le carrefour de la recherche et de l'innovation dans les transports terrestres, 10- 12 mai 2011, Bordeaux

Invitational Conference

DAVENNE D, La simulation comme outil d'étude des situations d'hypovigilance au volant, Colloque International du CIREVE « La réalité virtuelle au service de la recherche », Caen, les 27 et 28 janvier 2011

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