**TNO Defence, Security and Safety**

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek / Netherlands Organisation for Applied Scientific Research

Lange Kleiweg 137
P.O. Box 45
2280 AA Rijswijk

www.tno.nl

T +31 15 284 30 00
F +31 15 284 39 91
Info-DenV@tno.nl

**TNO report**

**TNO-DV 2006 A270**

# Sleep and alertness management III: effects of a nap and hypnotics on performance during the late evening, night and early morning in marmosets

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|---|---|
| Date | November 2006 |
| Author(s) | Dr. I.H.C.H.M. Philippens<br>R.A.P. Vanwersch<br>M.J. Jongsma, BSc<br>B. Groen<br>Dr. B.M. Bouwman |
| Classification report | Ongerubriceerd |
| Classified by | Kol. Vliegerarts J.L.A. van der Hoorn |
| Classification date | 10 October 2006<br>(This classification will not change) |
| Title | Ongerubriceerd |
| Managementuittreksel | Ongerubriceerd |
| Summary | Ongerubriceerd |
| Report text | Ongerubriceerd |
| Copy no | 7 |
| No. of copies | 19 |
| Number of pages | 24 (excl. RDP & distributionlist) |
| Number of appendices | - |



The classification designation Ongerubriceerd is equivalent to Unclassified, Stg. Confidentieel is equivalent to Confidential and Stg. Geheim is equivalent to Secret.

# Slaap- en alertheidsmanagement III: effecten van een dutje en slaapmiddelen op performance tijdens de avond, nacht en vroege ochtend in marmosetapen

## Probleemstelling

In opdracht van het Ministerie van Defensie wordt door TNO Defensie en Veiligheid onderzoek gedaan naar praktische richtlijnen om tijdens militaire missies ernstige vermoeidheid te voorkomen en de prestaties en alertheid te optimaliseren. Ervaringen met militaire missies hebben namelijk geleerd dat de nadelige effecten van slaaptekort een zeer belangrijke rol speelden bij de uitvoering van de missies. Aangezien tijdens militaire operaties de omstandigheden door omgeving en door de aard van de missie niet altijd optimaal zijn om spontaan de slaap te vatten zou het gebruik van kortwerkende slaapmiddelen een oplossing kunnen bieden.
Deze slaapmiddelen moeten niet alleen de inslaaptijd verkorten en bespoedigen en garant staan voor een goede slaapkwaliteit, maar ook de inzetbaarheid na waken niet nadelig beïnvloeden. Deze inzetbaarheid kan gemeten worden aan de hand van gedragsstudies waarbij taakverrichting en fysieke aspecten centraal staan.

## Beschrijving van de werkzaamheden

In een eerder uitgevoerd onderzoek voor het Ministerie van Defensie is een selectie gemaakt van mogelijk geschikte slaap- en alertheidsverhogende middelen [Busker *et al.*, TNO-rapport PML 2000-A2]. In het hier gerapporteerde onderzoek zijn van de geselecteerde kortwerkende slaapmiddelen temazepam, zolpidem en zaleplon de effecten op de inzetbaarheid na vroegtijdig wekken in een relevant diermodel onderzocht. Hiervoor is het slaapdeprivatiemodel in de marmosetaap ontwikkeld en gevalideerd waarna de taakverrichting met behulp van een hand-oogcoördinatietaak en de fysieke aspecten met behulp van een exploratie- en locomotoractiviteitstest zijn onderzocht. Deze testen zijn verricht op verschillende tijdstippen: tijdens late-avondsessies, nachtelijke sessies en vroege-ochtendsessies. Voor aanvang hebben de dieren een dutje mogen doen. Dit dutje was of spontaan of geïnduceerd via een slaapmiddel. Daarnaast is een groep getest zonder dutje in de late middag om de gedragseffecten van slaapdeprivatie te monitoren.

## Resultaten en conclusies

De resultaten van slaapdeprivatie op de hersenactiviteit laten zien dat de marmosetaap een goed model is voor onderzoek waarbij tijdverschuivingen binnen het circadiane ritme een rol spelen. Ook blijkt dat het gebruik van een dutje in de late middag een positief effect heeft op het tegengaan van de verminderde inzetbaarheid tijdens nachtelijke sessies. Dit is ook aangetoond in mensen en benadrukt de bruikbaarheid van dit model. Alle drie geselecteerde slaapmiddelen waren goed in staat om slaap te induceren. Na vroegtijdig wakker maken bleek het slaapmiddel zolpidem de inzetbaarheid niet nadelig te beïnvloeden. De performance was net zo goed als na een spontane dut. Ook zaleplon bleek een positief effect op de inzetbaarheid te hebben. Temazepam vertoonde ook enige verbetering op de performance maar niet op de activiteit en was minder effectief in het tegengaan van de vermindering van taakverrichting dan zaleplon en zolpidem. Vermoedelijk wordt dit veroorzaakt door het 'carry-over'-effect na gebruik van temazepam. Vooral tijdens de eerste sessie (late avond) van de taakverrichting was de performance minder goed, de twee latere sessies daarentegen waren wel verbeterd. Zolpidem verstoorde de taakverrichting en de activiteit het minst: er was zelfs geen afwijking met de placebo.

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Echter, de literatuur vermeldt dat zolpidem tot ongewenste persistente slaperigheid in vrouwen leidt wat de toepassing van dit middel zal limiteren. Daarom zal voor het slaap- en alertheidsmanagement tijdens militaire operaties het slaapmiddel zaleplon de voorkeur hebben boven zolpidem en temazepam.

## Toepasbaarheid

Het gebruik van slaapmiddelen om slaap te induceren en te optimaliseren met als doel de inzetbaarheid tijdens waak te verbeteren heeft alleen zin als het gebruik van de slaapmiddelen geen nadelig effect heeft op de inzetbaarheid na waken.

Van deze kort- en snelwerkende slaapmiddelen is bekend dat zij niet of nauwelijks het normale slaappatroon verstoren. Uit deze studie blijkt ook dat de inzetbaarheid na waken na gebruik van het slaapmiddel niet of nauwelijks verstoord wordt. Dit gegeven is van belang om tot een advies te komen over de inzetbaarheid van slaapmiddelen voor het optimaliseren van het slaap- en alertheidsmanagement.
Dit onderzoek naar aspecten van slaapdeprivatie, in nacht- en vroege-ochtendsessies, is bovendien zinvol voor de extrapolatie van de resultaten naar de mens.

| **PROGRAMMA** | **PROJECT** |
|---|---|
| Programmabegeleider<br>dr. J. van der Plas, MGFB/MGFB, Staf/beleidsondersteuning | Projectbegeleider<br>Kol. Vliegerarts J.L.A. van der Hoorn, Commando Luchtstrijdkrachten/Ho |
| Programmaleider<br>P.J.L. Valk, TNO Defensie en Veiligheid, BU Gedrag, Training en Prestatie | Projectleider<br>dr. I.H.C.H.M. Philippens, TNO Defensie en Veiligheid, BU Biologische en Chemische Bescherming, Diagnose en Therapie |
| Programmatitel<br>Arbeidsomstandigheden bij Defensie | Projecttitel<br>Slaap- en alertheidsmanagement |
| Programmanummer<br>V039 | Projectnummer<br>014.12840 |
| Programmaplanning<br>Start 01-01-2001<br>Gereed 31-12-2006 | Projectplanning<br>Start 01-01-2001<br>Gereed 31-12-2006 |
| Toezichthouder<br>- | |
| Frequentie van overleg<br>Met de programma/projectbegeleider werd achtmaal gesproken over de invulling en de voortgang van het onderzoek. | Projectteam<br>dr. I.H.C.H.M. Philippens; R.A.P. Vanwersch; M.J. Jongsma; BSc B. Groen; A. Strijkstra |

**ONGERUBRICEERD**

Contact en rapportinformatie

Lange Kleiweg 137
Postbus 45
2280 AA Rijswijk

T +31 15 284 30 00
F +31 15 284 39 91

**Info-DenV@tno.nl**

**TNO-rapportnummer**
TNO-DV 2006 A270

**Opdrachtnummer**
-

**Datum**
november 2006

**Auteur(s)**
dr. I.H.C.H.M. Philippens
R.A.P. Vanwersch
M.J. Jongsma, BSc
B. Groen
dr. B.M. Bouwman

**Rubricering rapport**
Ongerubriceerd

# Samenvatting

Het is eerder aangetoond dat een dutje voorafgaand aan een nachtelijke taak een goede strategie is om alertheidsverminderende effecten, als gevolg van verschuivingen van het circadiane ritme, te voorkomen. Echter, tijdens militaire operaties spelen diverse factoren een rol die het normaal inslapen belemmeren of hinderen. In die situaties kan het gebruik van slaapmiddelen nuttig zijn. Aangezien directe paraatheid na vroegtijdig wekken een vereiste kan zijn tijdens militair optreden is het belangrijk om slaapmiddelen te kiezen die niet tot zogenaamde 'post-nap hangovers' leiden waardoor de inzetbaarheid verminderd wordt.

In deze studie is de marmosetaap gevalideerd als diermodel voor het testen van effecten van stoffen op taakverrichting tijdens 'shift work' zoals in veel militaire operaties het geval is. Vervolgens zijn de effecten van geselecteerde slaapmiddelen op de taakverrichting tijdens late avond, nachtelijke en vroege ochtend missies getest.
Het is aangetoond dat de homeostasis in de marmosetaap na slaaponthouding gelijk is aan de homeostasis bij de mens: de slaapintensiteit na een nacht van slaaponthouding, die kan plaatsvinden tijdens nachtelijke of vroege ochtend missies, bleek toegenomen tijdens de eerste uren van slaap overeenkomstig met de situatie bij de mens. Ook blijkt een dutje voor de slaaponthouding de nadelige effecten op taakverrichting en activiteit aanzienlijk te verminderen zoals ook is waargenomen bij mensen. Om deze redenen kan aangenomen worden dat de marmosetaap een goed model is voor het testen van stoffen welke het slaap- en alertheidsniveau beïnvloeden.
De resultaten laten zien dat een dutje geïnduceerd door het slaapmiddel zolpidem minstens zo effectief is als een spontaan dutje om de afname in taakverrichting door de slaaponthouding tegen te gaan. Er waren geen resteffecten van het slaapmiddel gevonden. Een dutje met zaleplon bleek ook effectief te zijn. Temazepam vertoonde ook enige verbetering in het tegengaan van de vermindering van taakverrichting, maar was niet zo effectief als zaleplon en zolpidem. De literatuur vermeldt dat zolpidem tot ongewenste persistente slaperigheid in vrouwen leidt wat de toepassing van dit middel zal limiteren.
Daarom zal voor het slaap- en alertheidsmanagement in militaire operaties het slaapmiddel zaleplon de voorkeur hebben boven zolpidem en temazepam.

# Summary

It was already shown that napping before duty may be a good strategy to prevent performance decline during periods in which the circadian rhythm indicates the need to sleep. However, in a military setting, operational factors may prevent the onset and/or maintenance of restful sleep. In this case the use of hypnotics can be beneficial. Since immediate performance after premature waking can be required in a military setting it is important to choose hypnotics that do not result in so-called post-nap hangovers.
In this study, the marmoset monkey model was validated as a model for testing the effects of drugs on performance during time shift work as is the case in many military operations. Subsequently, the effect of hypnotics in the late afternoon on performance during late evening, night and early morning missions was tested.
It was proven that the homeostasis in marmoset monkeys after sleep deprivation is similar to the human homeostasis: The sleep intensity after a night of sleep deprivation, which will happen during late night or early morning duty, is increased in the first hours of sleep similar to human. Furthermore, a short nap by these animals before the sleep deprivation period can prevent most detrimental effects on performance and activity, as is the case in humans. Therefore, the marmoset monkey can be considered as a valid model for testing effects of drugs affecting the sleep and alertness behavior.

The results showed that a nap induced by the hypnotic zolpidem was at least equally effective as spontaneous napping in counteracting the sleep deprivation induced decline in performance. No residual effects of the hypnotic were found. A nap induced by zaleplon also showed to be effective in counteracting the sleep deprivation induced decline in performance. Temazepam showed some efficacy in counteracting the sleep deprivation induced decline in performance, but was not as effective as zolpidem and zaleplon. On the other hand, literature suggests that zolpidem leads to residual sleepiness in women which limits the applicability of the drug. This might indicate that for the management of sleep in a military setting the sleep inducing drug zaleplon should be preferred over zolpidem and temazepam.

# Contents

# 1 Introduction

Regular and good quality sleep is vital for proper performance and a healthy life. Disturbed sleep is hazardous and can have multiple causes. In a military setting situations that induce disturbed sleep frequently occur. Round the clock activity requires rapid work shift changes and long night duties, which provoke sleep loss and high stress levels. This may result in excessive sleepiness. These situations have been documented in a separate TNO report [Simons and Valk, 1999]. Recommended possible solutions with direct usefulness in crew endurance plans included strategic napping, chronobiological treatments and the use of sleep-inducing and wake-promoting drugs.

Any pharmacological intervention may result in unwanted side-effects. Sleep drugs induce sleep, but may also cause undesired carry-over effects, such as excessive sleepiness after sleep when wakefulness is required by situational demands. For sleep and alertness maintenance this means that a combination of a short acting hypnotic drug and a fast acting stimulant drug may be necessary in some situations.

An overview of sleep-inducing and wake-promoting drugs to aid sleep and to enhance alertness during military service has been given in other TNO reports [Simons and Valk, 1999; Busker *et al.*, 2000]. The Busker *et al.* [2000] report includes a literature study on the use of animal models for human sleep-wake management, and a theoretical evaluation of potential candidates, e.g. hypnotics ('downers') for sleep induction and stimulants ('uppers') for wake maintenance.

Hypnotics can be used at times when the situation may not allow spontaneous sleep induction. This can happen at times of the day in which the circadian rhythm dictates wakefulness or at moments of high arousal. Therefore, the effect of a nap in the late afternoon was tested on preventing performance decline during sleep deprivation. In cases the nap can not be induced spontaneously a hypnotic may help to speed up the sleep induction.

To investigate effects of drugs, animal studies are in several respects preferable over human studies. Drug research on human volunteers has practical and ethical problems, and more invasive studies are not possible at all in humans. Therefore, for the current study the marmoset monkey model was used.

First the comparability of sleep homeostasis of the marmoset will be compared with the human homeostasis to determine the usefulness of the marmoset monkey as a model for human purpose. This will be done by measuring the increased intensity of sleep after a 24-hours sleep deprivation.

In order to select the optimal sleep inducing drug for the management of sleep and wakefulness during evening and nighttime operations, the efficacy of such drugs in counteracting the effects of sleep deprivation on behavioral performance need to be investigated. Therefore, the effects of zolpidem, zaleplon and temazepam on behavioral performance were determined in the marmoset monkey during a night of sleep deprivation.

# 2 Materials and methods

## 2.1 Animals

Primates are our closest animal relatives. Therefore, intuitively, it appears that the chance that a monkey will react in a similar way to drugs as we do is much greater than when a rodent or guinea pig is used. Indeed, neuro-anatomical studies show, for example, that there is much similarity of the regional distribution through the hippocampus of several neurotransmitter receptor types of marmosets and humans than of rats and humans [Kraemer *et al.*, 1995]. The marmoset has been shown to be a suitable model for man in OP toxicity studies [Van Helden *et al.*, 1983].

Six adult male marmoset monkeys (*Callithrix jacchus; see Figure 1*), aged 2-6 years with initial body weights between 350-500 g were obtained from Harlan, United Kingdom. The monkeys were housed separately in cages (61 x 61 x 41 cm).
The ambient temperature in the housing room was regulated at 25 ± 2 °C and the relative humidity was maintained at > 60%. In this room a 12-hour day and night cycle was maintained. However, on the nights of sleep deprivation the light was kept on during the night. Daily they were fed with pellet chow, peanuts, fruit, boiled egg, baby biscuits, sunflower seeds, bread, beans, and fruit syrup after training or testing. Water was available *ad libitum*.
All aspects of animal care are described in Standard Operating Procedures, which are in agreement with current guidelines of the European Community. The independent TNO committee on Animal Care and Use approved all protocols for the animal experiments.

Figure 1 A picture of a marmoset monkey (*Callithrix jacchus*).

## 2.2 Drug administration

For the present study three sleep inducing drugs have been selected: zolpidem (3 mg/kg), zaleplon (10 mg/kg) and temazepam (15 mg/kg). The effective doses for the induction of sleep in marmoset monkeys were determined per drug by using a literature search, behavioral observations and pharmacokinetic analyses of the compounds (TNO-DV 2006 A268). All compounds were dissolved in fruit syrup (Karvan Cevitam) in a volume of 1 ml/kg, and were administered orally. The placebo was used as the placebo treatment.

## 2.3 Study design

### 2.3.1 *Effects on homeostasis during sleep deprivation*

To compare the sleep homeostasis in marmoset monkeys with the human homeostasis the increased intensity of sleep after a 24-hours sleep deprivation was measured. Sleep deprivation increases the necessity of sleep and thereby influences the homeostasis. Furthermore, does the sleep deprivation protocol of one night with no sleep and no sleep during daytime, which is also applied in human studies, not lead to an abnormal sleep intensity undershoot as found by small mammals like rodents [Franken *et al.*, 1991].

For this part of the study sleep induction was prevented by placing the animals in an automatic slow turning cage (15 rpm, 30 sec on and 30 sec off). During the stay in this cage food like apple was constant available. The electroencephalogram (EEG) for sleep analysis was measured by a telemetric device. For placing of the EEG electrodes on the skull see report TNO-DV 2006 A269. Furthermore, continue video registration was performed.

Day 1: 07:00 AM in turning cage until 18:45 PM.
19:00 PM in home cage (EEG measurements).
Day 2: 07:00 AM in turning cage until day 3 18:45 PM.
Day 3: 18:45 PM in home cage (EEG measurements) until day 4 8:00 AM.

### 2.3.2 *Effects of nap or hypnotics on performance during sleep deprivation*

Two hours before the end of the light period (late afternoon), the hypnotics or placebo was administered and the animals were allowed to have a nap for 4 hours (except for the placebo **no** nap group). This nap took place in individual chambers to prevent disturbance of the sleep. After these 4 hours the animals were placed in shared chamber and were kept awake during the dark period (night). On these test days the lights remained switched on during the dark period. Three times during the night the animals were tested on the Hand-eye coordination (HEC) task, to test the vigilance performance, followed by the Bungalow test, to measure the physical capabilities. The evening tests started at 20:30 h, the night tests started at 1:00 h and the morning tests started at 6:30 h (see Figure 2). On every test day and on every task/test the animals were tested in the same order.

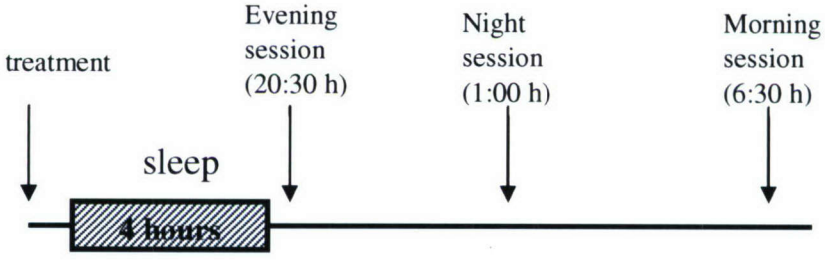


Figure 2 Schematic representation of the time course of the experiment. The placebo no nap group had the same time course, however, they were not allowed to sleep (they were kept awake during that time).

## 2.4 Hand-eye coordination task

The hand-eye coordination (HEC) is a sensitive task for measuring controlled motor movements and vigilance. An automated robot-guided apparatus with positive reinforcement as a motivating stimulus (small pieces of marshmallow) has been used to asses the HEC [Philippens *et al.* 2000]. The marmoset is placed in front of a test panel provided with a window (8 x 5 cm). A robot arm presents a reward behind the window.

An automated robot-guided apparatus using positive reinforcement as a motivating stimulus for the animals (small pieces of marshmallow) has been used to asses the Hand-eye coordination (HEC) [Philippens *et al.*, 2000]. The marmoset is placed in front of a test panel with a window (8 x 5 cm). A robot arm presents a reward behind the window (see Figure 3).

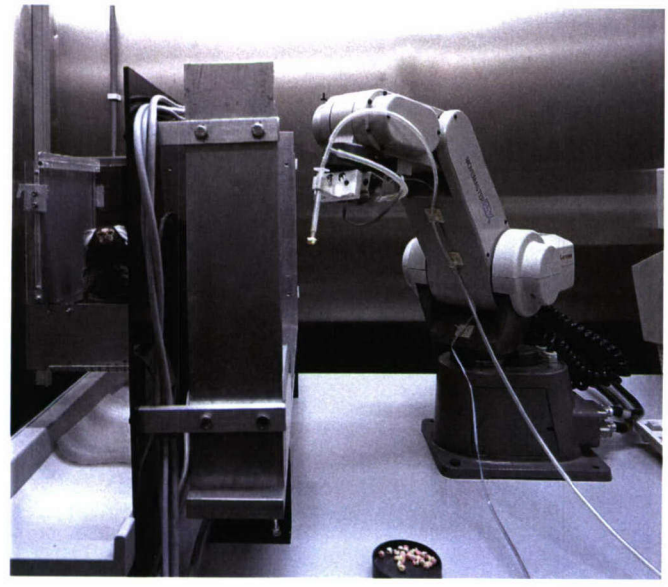

Figure 3 The setup of the hand-eye coordination (HEC) task.

The task existed of 42 trials. These 42 trials existed of three trial types: one using a non-moving reward in the middle of the window and two horizontally moving rewards at different speeds (0.04 and 0.08 m/s). Each type of trial was presented 14 times in one session. The animal was allowed one minute to grasp a non-moving reward.
At the beginning of each trial a sound signal was presented, intended to alert the animal. A pressure detector in the robot arm and infrared detectors in the window registered hits and attempts and speed of performance. A 'hit' was registered when the animal successfully retrieved the reward from the robot arm. The percentage of correct hits was used as a criterion to judge the performance of the animal. Before the start of the study, all animals were trained to collect at least 90% of the presented rewards.

## 2.5 Physical performance: loco-motor behavior

The levels of activity and exploratory behavior can play an important role in practically all measurements of animal behavior. A device called the 'Bungalow test' automatically and quantitatively assesses these parameters and is extensively described and validated [Wolthuis *et al.*, 1994; Philippens *et al.*, 2000]. The apparatus (see Figure 4) consists of

four horizontally placed non-transparent boxes (23 x 23 x 23 cm) all interconnected by 6 PVC tubes (inner diameter 9.5 cm).

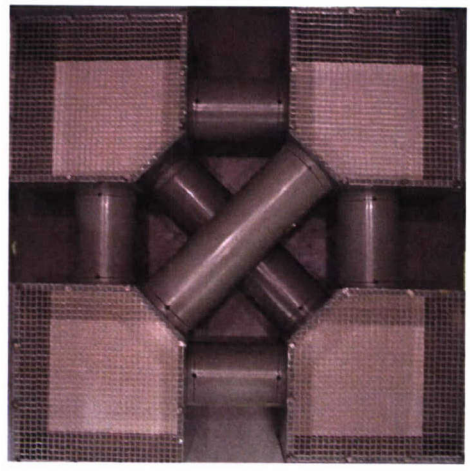

Figure 4 The setup of the bungalow task.

Each animal was placed in the same compartment at the start of each session.
The animals could move freely and change from one compartment to another during the 20-min session. A video tracking system (Ethovision, Noldus) registered the locomotor activity of the animal, expressed as the number of compartment changes during the session.

## 2.6 Statistics

The data were statistically analyzed using paired t-test procedures in SPSS (SPSS inc, Chicago, USA). Differences were considered to be statistically significant if $P<0.05$.

# 3 Results

## 3.1 Homeostasis effects during sleep deprivation

The main question is, does sleep deprivation increase the intensity of sleep after the deprivation as in human? Furthermore, does the sleep deprivation protocol of one night with no sleep en no sleep during daytime, which is also applied in human studies, not lead to an abnormal sleep intensity undershoot as found by small mammals like rodents [Franken *et al.*, 1991].

No problems were encountered by the induced motor activity in the turning cage.
The condition of the animal was not affected.
In Figure 5 the dynamics of the EEG power of the low frequency band (delta: 1-2 Hz) is shown. Under normal control baseline conditions (12 hour sleep deprivation), the EEG power of deep delta sleep increases during the first 3-6 hours tot the highest level. Thereafter, the power decreases again. After a sleep deprivation of 24 hours more, the EEG power starts at a higher level with its highest level between 1 and 4 hours. Comparable to baseline EEG, the power decreases after reaching the top at the same level. The relative increase (dotted line) of the delta power is highest during the first 2-4 hours.

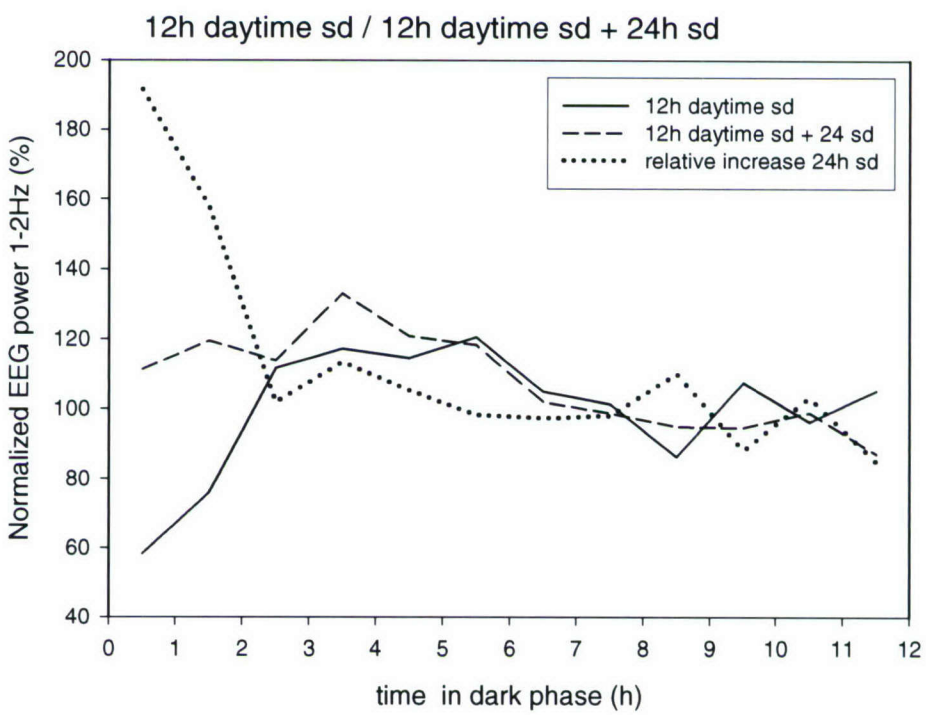


Figure 5 EEG power of 1-2 Hz (delta sleep) of normal baseline EEG (12h daytime sleep deprivation (sd)), or after 36 hour sleep deprivation (12h daytime sd + 24 sd). The dotted line indicate the relative increase of power during the first 2-4 hours of the sleep period after a sleep deprivation period.

## 3.2 Hand-eye coordination

### 3.2.1 *Effect of a nap*

Figure 6 shows the average number of correct responses on the HEC task after the placebo and the placebo no nap treatments. Statistical analyses show a significant decrease in HEC performance during the night ($P<0.05$) and morning ($P<0.05$) sessions in the placebo treated animals who were not allowed to take a nap (placebo no nap). Furthermore, no such decrease could be observed when the animals were allowed to take a nap, i.e. napping counteracted the sleep deprivation induced decline in HEC performance.

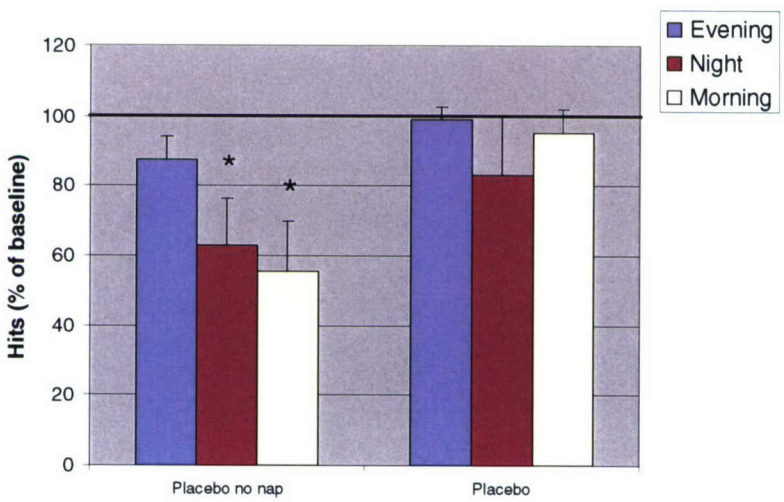


Figure 6 The effect of a nap in the afternoon on vigilance. The average hits as a percentage of baseline perfomance (+ SEM) on the hand-eye coordination (HEC) task for each of the test sessions after placebo, and placebo no nap treatments.
* indicate statistical significances compared to baseline.

When analyzing the data of the HEC performance per target speed (see Figure 8), the trend in the data persists. The HEC performance on the non-moving targets differed significantly from the baseline during the night ($P<0.05$) and morning ($P<0.05$) sessions for the placebo treated animals who were not allowed to nap. For this same group that did not have a nap a significant decrease could also be observed during the night session on the slow targets ($P<0.05$; morning session $P=0.052$) and during the morning session on the fast targets ($P<0.05$; night session $P=0.05$).

### 3.2.2 *Effect of a drug induced nap*

Figure 7 shows the average number of correct responses on the HEC task of animals that were allowed to nap after the placebo, zolpidem, zaleplon and temazepam treatments.

A significant decrease in HEC performance was observed during the evening session after temazepam ($P<0.05$). No other significant differences were observed, nevertheless a trend towards overall decreased HEC performance can be seen after temazepam, as well as a decreased performance during the morning session after zaleplon. Notably, after zolpidem HEC performance did not differ from baseline.

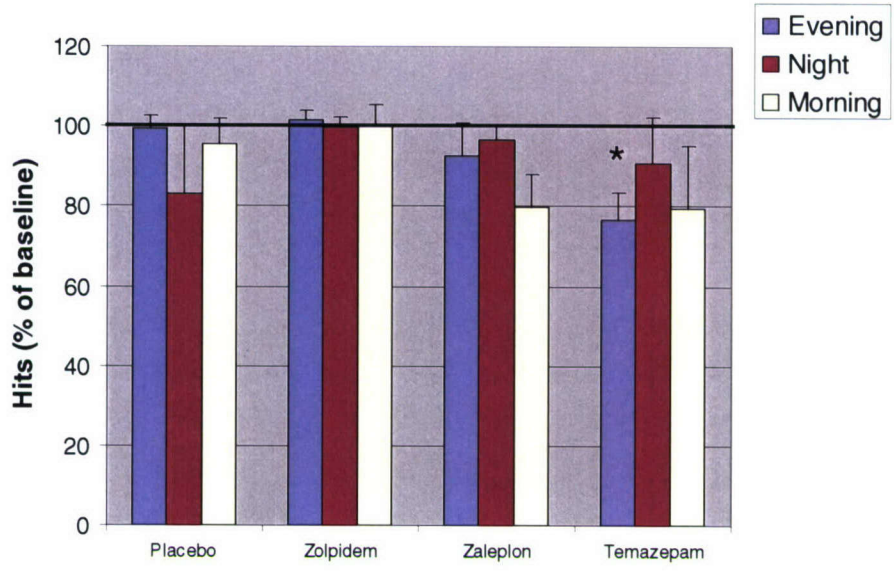


Figure 7 The average hits as a percentage of baseline perfomance (+ SEM) on the hand-eye coordination (HEC) task for each of the test sessions after placebo, zolpidem, zaleplon and temazepam treatment.
* indicate statistical significances compared to baseline.

When analyzing the data of the HEC performance per target speed (see Figure 8), the trends in the data persist. The HEC performance of animals after a nap on the non-moving targets significantly decreased during the morning session after zaleplon ($P<0.05$). Also, a significant decrease in performance on the moving targets (both low and fast speed) was observed during the evening session after temazepam ($P<0.05$).

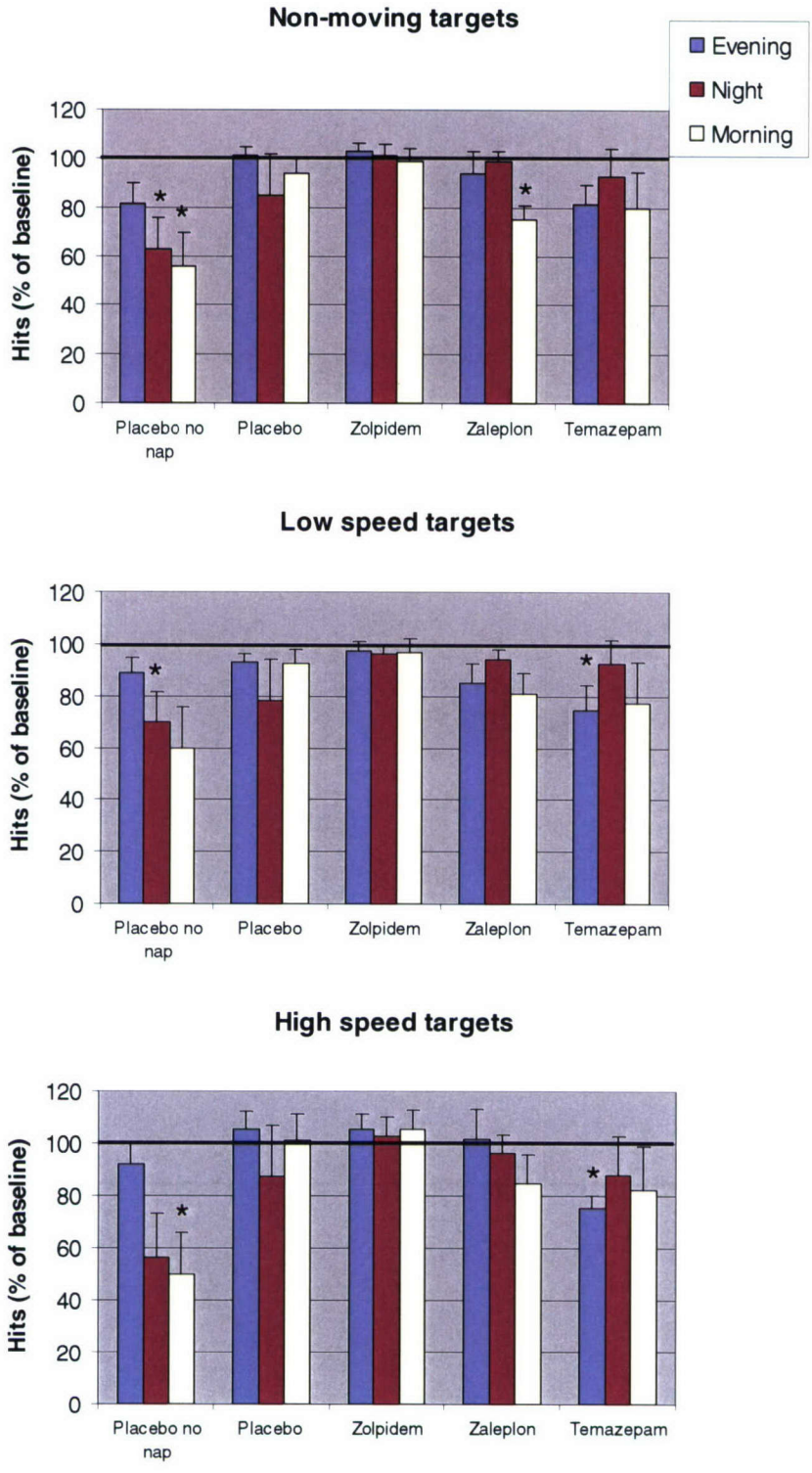


Figure 8 The average hits as a percentage of baseline perfomance (+ SEM) on the hand-eye coordination (HEC) task per target speed for each of the test sessions after placebo no nap, placebo, zolpidem, zaleplon and temazepam treatment.
* indicate statistical significances compared to baseline.

## 3.3 Physical performance: loco-motor behavior

### 3.3.1 *Effect of a nap*

Figure 9 shows the average number of compartment changes as percentage of baseline in the bungalow test after the placebo and the placebo no nap treatments.
Statistical analyses show a significant decrease in activity during the night ($P<0.05$) and morning ($P<0.05$) sessions in the placebo treated animals who were not allowed to take a nap (placebo no nap) as compared to both baseline and the evening session. The bungalow activity is also significantly lower on the morning test session as compared to baseline after placebo ($P<0.05$) treatment, i.e. napping only partly counteracts the sleep deprivation induced decline in activity.

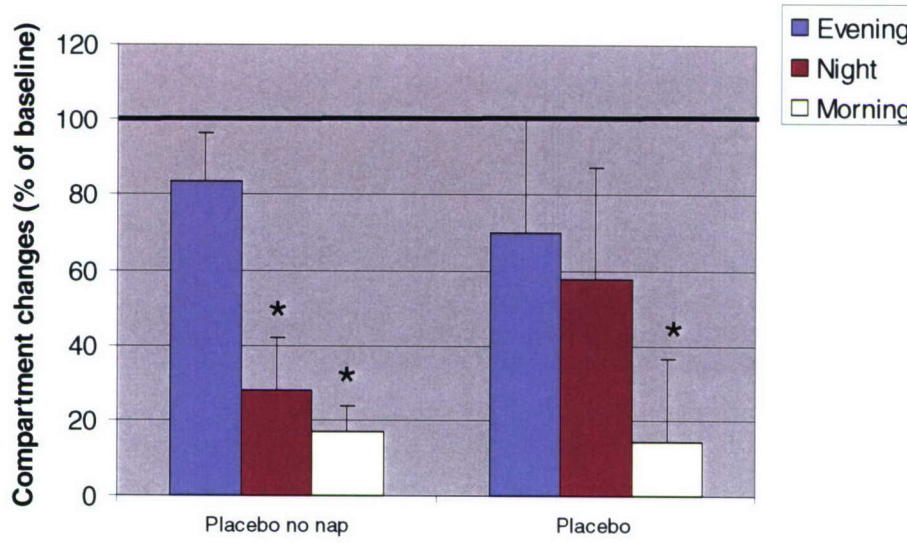


Figure 9 The effect of a nap in the afternoon on physical performance.The average compartment changes as a percentage of baseline (+ SEM) on the bungalow test for each of the test sessions after placebo and the placebo no nap treatments.
* indicate statistical significances compared to baseline.

### 3.3.2 *Effect of a drug induced nap*

Figure 10 shows the average number of compartment changes as percentage of baseline in the bungalow test after the placebo, zolpidem, zaleplon and temazepam treatments. After all the treatments a trend towards a general decrease in activity during the night can be observed. Furthermore, the observed decline seems to be mainly limited to the night and morning sessions. The bungalow activity is significantly lower on the morning test session as compared to baseline after placebo ($P<0.05$), zolpidem ($P<0.05$), zaleplon ($P<0.05$) and temazepam ($P<0.05$) treatments. After temazepam the bungalow activity is also significantly lower on the night test session as compared to baseline ($P<0.05$). Also, the bungalow activity is significantly lower on the morning test session as compared to evening session after zolpidem ($P<0.05$), zaleplon ($P<0.05$) and temazepam ($P<0.05$) treatments. After zolpidem the bungalow activity on the night test session is also significantly lower than on the evening session, whereas after temazepam a non-significant trend towards such an effect was observed ($P=0.053$).

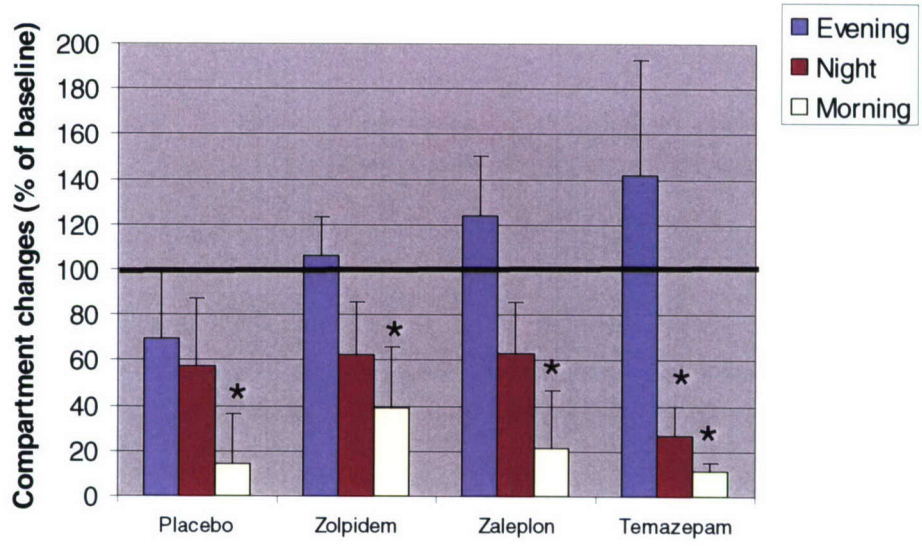


Figure 10 The average compartment changes as a percentage of baseline (+ SEM) on the bungalow test for each of the test sessions after placebo, zolpidem, zaleplon and temazepam.
* indicate statistical significances compared to baseline.

# 4 Discussion

## 4.1 Validation of sleep deprivation effects

Sleep is a behavior that is regulated by minimal two processes as described in the 2-processes model [Daan *et al.*, 1984]. There is one process that regulates the daily timing of sleep (process C, circadian) and there is a process which is a derivative of the sleep process itself (process S, sleep). Process C is regulated by the inner biological clock and process S is dependent of the necessity of sleep.
To measure the homeostasis of sleep, sleep deprivation is often used. This increases the necessity of sleep. In many animals (inclusive human) the induction of sleep deprivation is possible. However, the reaction on this sleep deprivation can vary within species, which dependents on the presence of sleep deprivation in their normal habit.

The question is whether the effects of sleep deprivation in marmosets are similar to other mammals like human: does sleep deprivation increase the intensity of sleep after the deprivation? Furthermore, does the sleep deprivation protocol of one night with no sleep en no sleep during daytime, which is also applied in human studies, lead to an abnormal sleep intensity undershoot as found by small mammals like rodents [Franken *et al.*, 1991].
Indeed the highest relative increase of delta power was found during the first 2-4 hours. This means that after sleep deprivation the sleep intensity is increased during the first hours of sleep. This is in agreement with the expectations based on sleep regulation [Daan *et al.*, 1984].

On behavioral level the results of the placebo no nap group show that during sleep deprivation the performance on the HEC task as well as the activity in the bungalow task decreases over night as was the case in an earlier study (TNO-DV 2006 A270). Accordingly, sleep deprivation effects on performance have been observed in other species and humans [Rogers *et al.*, 2003; Silva *et al.*, 2004; Porrino *et al.*, 2005; Blatter *et al.*, 2006]. Furthermore, in this animal study it was shown that the sleep deprivation induced effects on performance and activity can be at least partially counteracted by napping, as is the case in humans [Batéjat and Lagarde, 1999; Philip *et al.*, 2006].

The demonstration of such sleep deprivation effects and the (partial) counteraction of these by napping, as demonstrated in this study, shows that the marmoset monkey can be considered to be a valid animal model for sleep deprivation.

## 4.2 Effects of hypnotics

It was shown that sleep deprivation induced effects on performance can be (partially) counteracted by napping [present study; Batéjat and Lagarde, 1999; Philip *et al.*, 2006]. However, in a military setting sleep opportunities are available but can be comprised due to operational factors that prevent the onset and/or maintenance of restful sleep. In this case the use of hypnotics can be beneficial. Since immediate performance after premature waking can be required in a military setting it is important to choose hypnotics that do not result in so called post-nap hangovers.

### 4.2.1 *Napping*

The efficacy of napping (and the hypnotics) was most optimal for the performance on the HEC task. This could be explained by the fact that the bungalow task is a task in which physical activity is not demanded nor evoked, which is in contrast to the activity evoking HEC task. It is likely that the animals took the time they spent in the bungalow task to take some rest, resulting in few compartment changes. Since the bungalow task always followed the HEC task, the performance on the HEC task was not affected by the behavior of the animals during the bungalow task.

### 4.2.2 *Zolpidem*

A previous study showed that all the sleep inducing drugs were effective in inducing sleep, i.e. the animals went to sleep quickly after administration (TNO-DV 2006 A269). This study showed that the hypnotic zolpidem was at least equally effective as spontaneous napping in counteracting the sleep deprivation induced decline in (HEC) performance. Similar efficacy of zolpidem has also been observed in humans [Caldwell and Caldwell, 1998; Caldwell and Caldwell, 2005; Batéjat *et al.,* 2006]. Furthermore, it has been shown that zolpidem can be effectively combined with alertness enhancer caffeine or modafinil for maintaining performance [Batéjat *et al.,* 2006]. However, zolpidem is believed to cause significant residual sedation in women which limits the applicability of the drug [Nicholson and Stone, 1999].

### 4.2.3 *Zaleplon*

A nap induced by zaleplon also showed to be effective in counteracting the sleep deprivation induced decline in performance. Furthermore, the elimination half-life of zaleplon was shown to be shorter than that of zolpidem in both marmoset monkeys (TNO-DV 2006 A268) and humans [Greenblatt *et al.,* 1998; Sanchez Garcia *et al.,* 2000]. Having a short elimination half-life is considered to be a favorable property of a hypnotic since it limits the likelihood of occurrence of post-nap hangovers. For the choice in the ideal compound for the induction of sleep also the more practical issues come into play. Regarding zaleplon there is the practical issue of availability, namely, despite the approval by the CBG (College ter Beoordeling van Geneesmiddelen) zaleplon is not yet licensed for sale in The Netherlands.

### 4.2.4 *Temazepam*

Temazepam showed to have some efficacy in counteracting the sleep deprivation induced decline in performance, but was not as effective as zolpidem and zaleplon. This could be the result of temazepam induced residual sedation after premature waking. Accordingly, the elimination half-life of temazepam was shown to be longer than that of zaleplon and zolpidem in humans [Jochemsen *et al.,* 1983; Lockniskar and Greenblatt, 1990]. Thus, temazepam is a good choice when a prolonged hypnotic effect is desired as long as there is relative certainty that the hypnotic-induced sleep period will not be unexpectedly truncated [Caldwell and Caldwell, 2005].

# 5 Conclusion

Napping counteracts the sleep deprivation induced declines in performance. However, in a military setting sleep opportunities are available but can be comprised due to operational factors that prevent the onset and/or maintenance of restful sleep. The present study showed that in this case the use of zolpidem or zaleplon can be beneficial. A nap induced by temazepam was also shown to have some benefits, but was not as effective as zolpidem or zaleplon. This may be a result of the carry-over effects which was found on the sleep pattern after temazepam. On the other hand, literature suggests that zolpidem leads to residual sleepiness in women which limits the applicability of this drug. This might indicate that for the management of sleep in a military setting the sleep inducing drug zaleplon should be preferred over zolpidem and temazepam.

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# 7 Signature

Rijswijk, November 2006

TNO Defence, Security and Safety

J. Schaafsma, MSc
Group leader

Dr. I.H.C.H.M. Philippens
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# REPORT DOCUMENTATION PAGE
(MOD-NL)

| 1. DEFENCE REPORT NO (MOD-NL) | 2. RECIPIENT'S ACCESSION NO | 3. PERFORMING ORGANIZATION REPORT NO |
|---|---|---|
| TD2006-0058 | | TNO-DV 2006 A270 |
| **4. PROJECT/TASK/WORK UNIT NO** | **5. CONTRACT NO** | **6. REPORT DATE** |
| 014.12840 | - | November 2006 |
| **7. NUMBER OF PAGES** | **8. NUMBER OF REFERENCES** | **9. TYPE OF REPORT AND DATES COVERED** |
| 24 (excl RDP & distribution list) | 26 | Final |

**10. TITLE AND SUBTITLE**

Sleep and alertness management III: effects of a nap and hypnotics on performance during the late evening, night and early morning in marmosets

**11. AUTHOR(S)**

Dr. I.H.C.H.M. Philippens, R.A.P. Vanwersch, M.J. Jongsma, BSc, B. Groen, Dr.B.M. Bouwman

**12. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)**

TNO Defence, Security ans Safety, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Lange Kleiweg 137, Rijswijk, The Netherlands

**13. SPONSORING AGENCY NAME(S) AND ADDRESS(ES)**

HWO-CO, P.O. Box 20701, 2500 ES The Hague, The Netherlands

**14. SUPPLEMENTARY NOTES**

The classification designation Ongerubriceerd is equivalent to Unclassified.

**15. ABSTRACT (MAXIMUM 200 WORDS (1044 BYTE))**

Napping before duty may be a good strategy to prevent performance decline during periods in which we normally sleep. However, operational factors may prevent the onset and maintenance of restful sleep. Therefore, hypnotics can be beneficial. Since immediate performance after premature waking can be required in a military setting it is important that hypnotics do not result in post-nap hangovers. After validation of the marmoset model, the effect of hypnotics in the late afternoon on performance during late evening, night and early morning was tested. The results showed that a nap induced by zolpidem was at least equally effective as spontaneous napping in counteracting the sleep deprivation induced decline in performance. No residual effects of the hypnotic were found. A nap induced by zaleplon was also effective in counteracting the decline in performance. Temazepam showed some efficacy in counteracting the sleep deprivation induced decline in performance, but was not as effective as zolpidem and zaleplon. On the other hand, literature suggests that zolpidem leads to residual sleepiness in women which limits the applicability of the drug. This might indicate that for the management of sleep in military operations the hypnotic zaleplon should be preferred over zolpidem and temazepam.

**16. DESCRIPTORS**

| | | | |
|---|---|---|---|
| Alertrness | Behavior | Monkeys | Sleep |
| Animals | Hypnotics | Performance | |

| 17a.SECURITY CLASSIFICATION (OF REPORT) | 17b.SECURITY CLASSIFICATION (OF PAGE) | 17c.SECURITY CLASSIFICATION (OF ABSTRACT) |
|---|---|---|
| Ongerubriceerd | Ongerubriceerd | Ongerubriceerd |

| 18. DISTRIBUTION AVAILABILITY STATEMENT | 17d.SECURITY CLASSIFICATION (OF TITLES |
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