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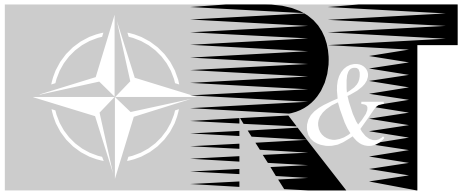


RESEARCH AND TECHNOLOGY ORGANISATION

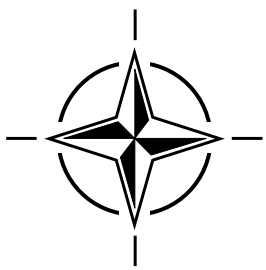
BP 25, 7 RUE ANCELLE, F-92201 NEUILLY-SUR-SEINE CEDEX, FRANCE

RTO LECTURE SERIES 223

Sleep/Wakefulness Management in Continuous/Sustained Operations

(La gestion des rythmes veille/sommeil lors des opérations continues/soutenues)

The material in this publication was assembled to support a Lecture Series under the sponsorship of the Human Factors and Medicine Panel (HFM) and the Consultant and Exchange Programme of RTO presented on 17-18 June 2002 in Fort Rucker, Alabama, United States, on 24-25 June 2002 in Warsaw, Poland, and on 27-28 June 2002 in Paris, France.



Published November 2002

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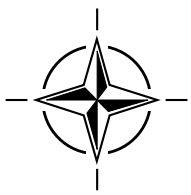

The Research and Technology Organisation (RTO) of NATO

RTO is the single focus in NATO for Defence Research and Technology activities. Its mission is to conduct and promote cooperative research and information exchange. The objective is to support the development and effective use of national defence research and technology and to meet the military needs of the Alliance, to maintain a technological lead, and to provide advice to NATO and national decision makers. The RTO performs its mission with the support of an extensive network of national experts. It also ensures effective coordination with other NATO bodies involved in R&T activities.

RTO reports both to the Military Committee of NATO and to the Conference of National Armament Directors. It comprises a Research and Technology Board (RTB) as the highest level of national representation and the Research and Technology Agency (RTA), a dedicated staff with its headquarters in Neuilly, near Paris, France. In order to facilitate contacts with the military users and other NATO activities, a small part of the RTA staff is located in NATO Headquarters in Brussels. The Brussels staff also coordinates RTO's cooperation with nations in Middle and Eastern Europe, to which RTO attaches particular importance especially as working together in the field of research is one of the more promising areas of initial cooperation.

The total spectrum of R&T activities is covered by the following 7 bodies:

- AVT Applied Vehicle Technology Panel
- HFM Human Factors and Medicine Panel
- IST Information Systems Technology Panel
- NMSG NATO Modelling and Simulation Group
- SAS Studies, Analysis and Simulation Panel
- SCI Systems Concepts and Integration Panel
- SET Sensors and Electronics Technology Panel

These bodies are made up of national representatives as well as generally recognised 'world class' scientists. They also provide a communication link to military users and other NATO bodies. RTO's scientific and technological work is carried out by Technical Teams, created for specific activities and with a specific duration. Such Technical Teams can organise workshops, symposia, field trials, lecture series and training courses. An important function of these Technical Teams is to ensure the continuity of the expert networks.

RTO builds upon earlier cooperation in defence research and technology as set-up under the Advisory Group for Aerospace Research and Development (AGARD) and the Defence Research Group (DRG). AGARD and the DRG share common roots in that they were both established at the initiative of Dr Theodore von Kármán, a leading aerospace scientist, who early on recognised the importance of scientific support for the Allied Armed Forces. RTO is capitalising on these common roots in order to provide the Alliance and the NATO nations with a strong scientific and technological basis that will guarantee a solid base for the future.

Published November 2002

ISBN 92-837-1073-8

Printed by St. Joseph Print Group Inc.
(A St. Joseph Corporation Company)
1165 Kenaston Street, Ottawa, Ontario, Canada K1G 6S1

Sleep/Wakefulness Management in Continuous/Sustained Operations

(RTO EN-016 / HFM-064)

Executive Summary

Synthesis

1. The first lecture emphasises that a soldier is, first of all, a human being. If he fails to respect his biological rhythms, his vigilance and performance deteriorate. During sustained/continuous operations (SUSOPS and CONOPS), this may compromise successful mission completion. If we want to preserve the soldier in these potentially hazardous operational conditions, the sleep/wakefulness cycle should be managed as well as possible.
2. The second lecture emphasises the importance of individual differences. These are due to specific sleep characteristics, the level of training in SUSOPS and CONOPS, and the knowledge we have of our own capability to alleviate the effects of sleep loss or jet lag syndrome.
3. The third lecture describes the penalising effects of sleep deprivation. First, the methods that are available to measure sleepiness and fatigue are described. Then, the effects of fatigue on performance are highlighted. Overall, sleep deprivation adversely affects performance, but the degree to which it does so depends on the nature and duration of the task, and on the amount of prior wakefulness.
4. The fourth lecture concerns the effects of jet-lag. The symptoms begin to occur with four hours of jet lag and increase in quantity and intensity with jet lags of up to twelve hours. Jet lag effects depend on the direction of the flight and on environmental and individual parameters. Jet lag is caused by desynchronisation of the biological rhythms compared to the external synchroniser (“Zeitgeber”).
5. The fifth lecture focuses on measures to counteract the effects of SUSOPS and CONOPS. A very natural measure is to take a nap. Napping strategies are described. After naps, the sleep inertia period has to be taken into account.
6. Physiological and pharmacological countermeasures are presented in the sixth lecture. Food containing high quantities of glucose and lipids increase drowsiness. Conversely, small meals containing high quantities of protein increase vigilance. Physical exercise may be helpful, and the influence of light has also been demonstrated. Pharmacological approaches are compounded by the fact that the effects of drugs may vary across individuals, and may be modified by stress, heat or cold, etc. Therefore, the use of medication should be restricted as much as possible, and possible side effects on task performance should be taken into account. The challenge is to prescribe a safe and effective substance.
7. In the seventh lecture, the advantages but also the side effects of amphetamines are discussed.
8. In the eight lecture, a new galenic form of caffeine is introduced and its interest in SUSOPS and CONOPS is demonstrated.
9. Modafinil, a new and very powerful substance, is introduced in the ninth lecture. It appears to enhance vigilance as powerfully as amphetamine, without its side effects, but the prescription of this substance is still reserved for the treatment of specific diseases.
10. Hypnotic substances are also used for sleep-wakefulness management. The tenth lecture discusses benzodiazepines and non-benzodiazepines, and their properties and side effects are highlighted.
11. Strategies to alleviate jet-lag are presented in the eleventh and last lecture. Measures like phototherapy and adapted social environments are discussed, and problems associated with the use of chronobiotic substances (e.g., melatonin) are examined.

Recommendations

1. The physiology of the sleep-wakefulness cycle should be respected as much as possible.
2. It is recommended to have a thorough knowledge of the physiology of sleep-wakefulness cycle and of one's own capabilities.
3. The best remedy against sleep loss is sleep: physiological countermeasures should be used as a first step.
4. If more is needed, medical advice should be sought in order to determine the best pharmacological aid, in the context of the future operational situation.

Concluding Remarks

We spend a third of our life sleeping. We need to properly manage the sleep-wakefulness cycle in our daily life as well as in SUSOPS and CONOPS in order to keep our vigilance and performance levels optimal. We are responsible for our own safety and sometimes for that of our crews and friends. We have to be persuaded of the importance of the sleep-wakefulness cycle management in SUSOPS and CONOPS and we have also to persuade our colleagues, as well as our commanders of this reality.

La gestion des rythmes veille/sommeil lors des opérations continues/soutenues

(RTO EN-016 / HFM-064)

Synthèse

Synthèse

1. La première conférence met l'accent sur le fait que le combattant est avant tout un être humain. S'il ne respecte pas ses rythmes biologiques, sa vigilance et ses performances vont se détériorer. Au cours d'opérations continues (CONOPS) et soutenues (SUSOPS) cela peut mettre en cause le succès de la mission. Si nous voulons protéger le combattant dans cet environnement opérationnel potentiellement dangereux, le cycle veille/sommeil doit être géré le mieux possible.
2. La deuxième conférence souligne l'importance des différences entre individus. Elles sont dues à des caractéristiques de sommeil très spécifiques, mais aussi au niveau d'entraînement aux CONOPS et SUSOPS et enfin à la connaissance de chacun de ses propres capacités susceptibles de limiter les effets de la perte de sommeil ou du décalage horaire.
3. La troisième conférence permet de décrire les effets pénalisants de la perte de sommeil. Les méthodes disponibles pour mesurer la somnolence et la fatigue sont présentées avant de voir l'incidence de la fatigue sur les performances. D'une façon générale, la perte de sommeil a un effet négatif sur les performances mais suivant un degré qui dépend de nature et de la durée de la tâche et de la longueur de la période d'éveil précédente.
4. La quatrième conférence a pour sujet le décalage horaire. Les symptômes commencent à apparaître à partir de 4 heures de décalage et augmentent en quantité et en intensité jusqu'à des décalages de 12 heures. Les effets du décalage horaire dépendent de la direction du vol (est ou ouest), de l'environnement et de paramètres individuels. Le décalage horaire est dû à la désynchronisation des rythmes biologiques confrontés à une synchronisation extérieure (« Zeitgeber »).
5. Le sujet de la cinquième conférence porte sur les mesures pour contrer les effets des CONOPS/SUSOPS. La première mesure naturelle est de faire une sieste et des conseils sur les meilleures façons de faire la sieste sont présentés tout en sachant que la période d'inertie qui suit toute sieste doit être prise en compte.
6. Les contre mesures physiologiques et pharmacologiques sont abordées au cours de la sixième conférence. Une alimentation riche en glucose et lipides facilite la somnolence et réciproquement, des repas légers avec une forte teneur en protéines contribuent à la vigilance. Tout exercice physique peut être utile tout comme la lumière dont l'influence sur le sommeil a été démontrée. Les approches pharmacologiques sont rendues complexes par le fait que les effets des médicaments varient d'un individu à l'autre et peuvent être modifiés par le stress, la chaleur ou le froid etc. L'usage des médicaments doit donc être limité au maximum, en prenant bien en compte l'incidence des effets secondaires sur les performances. La difficulté est de prescrire une substance à la fois efficace et sure.
7. Les avantages mais aussi les effets secondaires des amphétamines sont abordés dans la septième conférence.
8. Au cours de la huitième intervention, une nouvelle forme naturelle de caféine est présentée avec la démonstration de ses effets en opérations continues / soutenues.
9. Un nouveau produit très efficace, le Modafinil est présenté lors de la neuvième conférence. Il apparaît comme un stimulateur de vigilance aussi puissant que les amphétamines mais sans effets secondaires. La prescription d'une telle substance reste cependant réservée au traitement de maladies bien spécifiques.
10. Les produits hypnotiques sont également utilisés dans la gestion des rythmes éveil/sommeil. La dixième conférence fait le point des benzodiazepines et non-benzodiazepines en soulignant leurs propriétés ainsi que leurs effets secondaires.

11. Des conseils pour contrer le décalage horaire sont présentés dans la onzième et dernière conférence. Des mesures comme la photo-thérapie et des environnements sociaux adaptés pourront faire l'objet de discussions et les problèmes liés à l'utilisation de substance chronobiotiques (comme la mélatonine) seront examinées.

Recommandations

1. La physiologie du cycle éveil/sommeil doit être respectée dans toute la mesure du possible.
2. Pour les combattants, il est recommandé d'avoir une connaissance approfondie de la physiologie de leurs cycles éveil/sommeil mais aussi de leurs capacités propres.
3. Le meilleur remède contre la perte de sommeil reste le sommeil et dans un premier temps, il est souhaitable de n'utiliser que des mesures physiologiques.
4. Si elles se révèlent insuffisantes, il faut solliciter un avis médical de façon à trouver l'aide pharmacologique la plus adaptée au contexte de l'environnement opérationnel.

Conclusion

Nous passons plus d'un tiers de notre vie à dormir. Il nous faut gérer d'une manière optimale notre cycle éveil/sommeil dans la vie courante comme dans les opérations continues ou soutenues de manière à garder notre vigilance et nos performances au plus haut niveau. Nous sommes responsables de notre propre sécurité et parfois de la sécurité des équipages et des amis qui nous sont confiés. Nous devons être conscients de l'importance de la gestion des cycles éveil/sommeil lors d'opérations continues et soutenues et il est de notre devoir d'en persuader non seulement nos collègues mais également nos responsables.

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† Abstract text for this paper can be found immediately following Paper 10.

List of Authors/Lecturers

Lecture Series Director: Méd. Chef Didier LAGARDE
Adjoint au Chef du Département
Facteurs Humains et Sciences Médicales
DGA/DSP/STTC/SH
26 Boulevard Victor
00457 Armées
FRANCE

COURSE LECTURERS

Dr. Ross A. PIGEAU
DCIEM
1133 Sheppard Avenue, West
P.O. Box 2000
Toronto
Ontario M3M 3B9
CANADA

Dr. Maria CASAGRANDE
Department of Psychology
University of Rome
La Sapienza, via dei Marzi, 78
00185 Rome
ITALY

Dr. Barbara M. STONE
QINETIC Centre for Human Sciences
Cody Technology Park
Bldg. A50, Ively Road
Farnborough, Hants GU14 OLX
UNITED KINGDOM

Dr. John A. CALDWELL
USAARL
Attn: MCMR-USA-AF (Caldwell)
PO Box 620577
Fort Rucker
AL 36362-0577
UNITED STATES

Dr. J. Lynn CALDWELL
USAARL
Attn: MCMR-USA-AF (Caldwell)
PO Box 620577
Fort Rucker
AL 36362-0577
UNITED STATES

CO-AUTHORS

Dr. Maurice BEAUMONT
Institut de Médecine Aérospatiale IMASSA
BP 73
91223 Bretigny/Orge
FRANCE

Dr. Bruno SICARD
Marine Nationale Antenne Programme
Etat Major
83800 Toulon Naval
FRANCE

Dr. Françoise CHAUFFARD
NESTEC Centre de recherche Nestlé
Vers-Chez-Les-Blanc 1000
Lausanne 26
SWITZERLAND

Dr. J. Lynn CALDWELL
USAARL
Attn: MCMR-USA-AF (Caldwell)
PO Box 620577
Fort Rucker
AL 36362-0577
UNITED STATES

Dr. Kecia K. HALL
U.S. Army Safety Center
Operations Research and
Statistical Analysis Division
Bldg 4905, Fifth Avenue
Fort Rucker
AL 36362-5363
UNITED STATES

Mr. Brian F. PRAZINKO
USAARL
Attn: MCMR-USA-AF (Caldwell)
PO Box 620577
Fort Rucker
AL 36362-0577
UNITED STATES

Introduction-Overview : The Sleep-Wakefulness Cycle and the SUSOPS/CONOPS

Médecin en Chef Didier Lagarde
Adjoint au Chef du Département
Facteurs Humains et Sciences Médicales
DGA/DSP/STTC/SH
26 boulevard Victor
00460 Armées
France

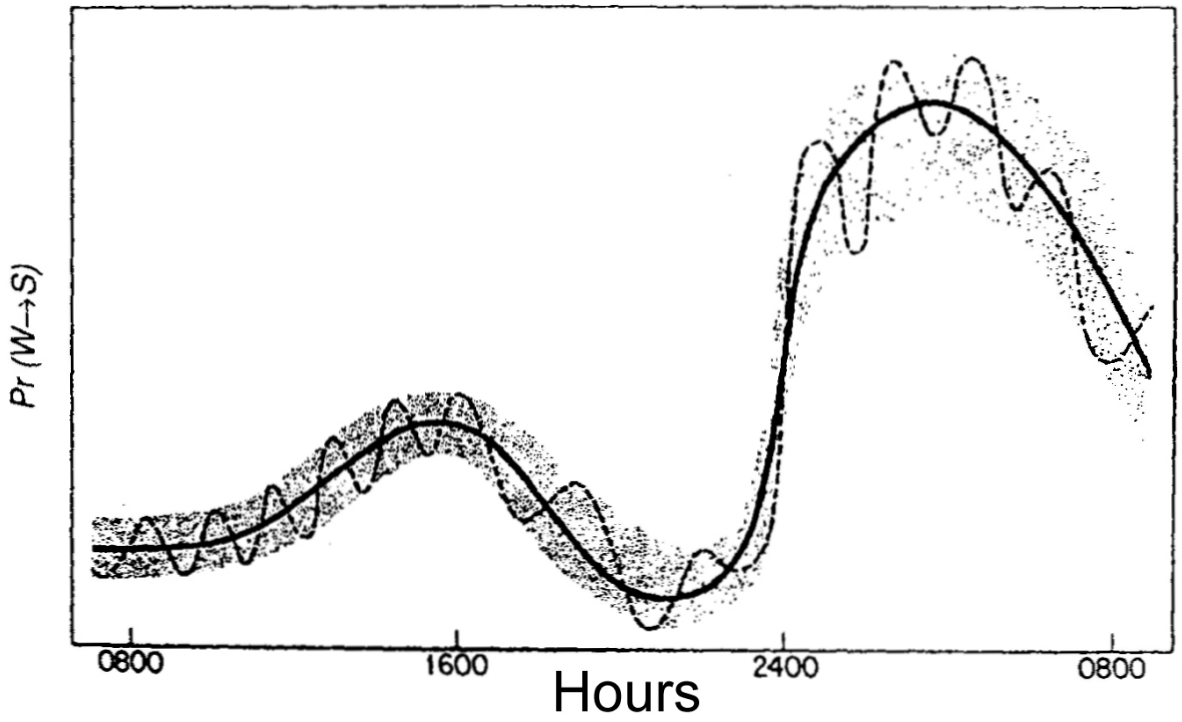
INTRODUCTION

Military operations in general and air operations in particular , are characterized by the need to maintain constant high levels of performance . Human performance is modified negatively by changes in schedule , sleep loss , transmeridian flights and continuous or sustained operations . Flight surgeons and other medical staff need to know how to assess and manage these challenges to operational efficiency. A recent NATO/RTO/HFM meeting identified the advances made in sleep-wakefulness management. The rapid deployment of military personnel across several time zones for sustained operations such as the recent air campaign in Kosovo , is a major challenge for sleep-wakefulness management. Different strategies are required to maintain operational efficiency at its highest level. They include , but are not limited to , adjustment of work schedules , sleep hygiene , napping and the controlled use of pharmacological agents. In order to enable the Alliance to continue to carry out this type of operation , scientific progress in this field must be communicated to military physicians in the field and the challenges presented should be understood by commanders both in the field and at headquarters ; it's the main goal of this Lecture series .We have to inform all military medical personnel and all military operational personnel of the practice of sleep-wakefulness management, by clearly demonstrating the positive and negative aspects of the measures employed.
To demonstrate the imperious need to know how to manage the sleep-wakefulness cycle , we have first to describe the physiology ,i.e. the normal use of one of the most important circadian biological rhythm of the body which is the sleep-wakefulness cycle . Then we will present the very frequent war situations that are susops (sustained operations) and conops (continuous operations) on a physiological point of view. At least we will observe the antinomy between the physiological use and the operational use of this very important circadian rhythm and by this way we will show the imperious necessity to manage the sleep-wakefulness cycle to maintain the efficiency and the security of the soldier.

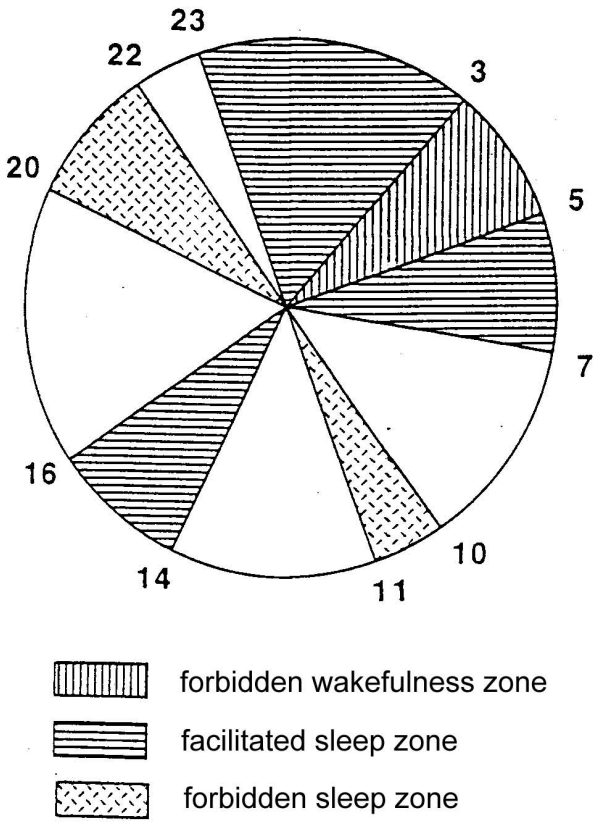
THE SLEEP-WAKEFULNESS CYCLE

The sleep-wakefulness cycle belongs to the biological rhythms. Is a circadian rhythm , because its period is around 24 hours (Reinberg 1959). An other characteristic of a circadian rhythm is its amplitude with an acrophase and a batyphase , which correspond to a hypovigilance period and a hypervigilance period. We can distinguish two hypovigilance periods (nocturnal between 02h00 and 04h00 ; diurnal between 14h00 and 16h00) and two hypervigilance periods (nocturnal between 20h00 and 22h00 ; diurnal between 10h00 and 12h00) . We call also the evolution of the vigilance : the sleep propensity (see figure from Lavie in Billiard [1]).These periods are determined by the MSLT (Multiple Sleep Latency Test) validated by Hélène Carskadon [2].

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

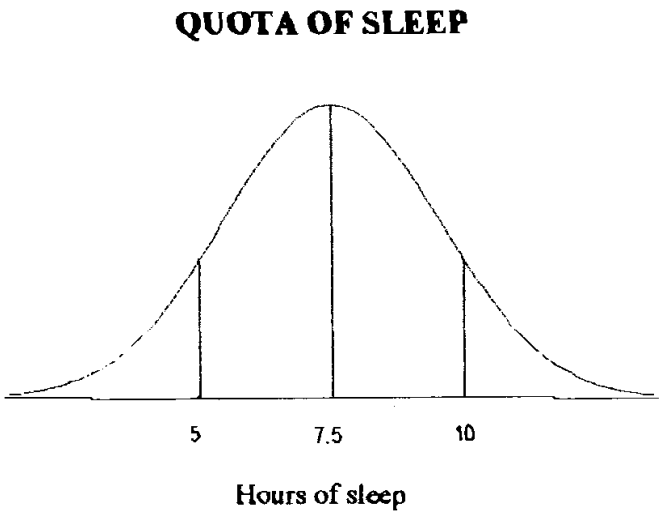


According to Peretz Lavie [3] is possible to define « forbidden sleep periods » and « facilitated sleep periods » , which correspond with periods where the subject take a long time before falling a sleep and periods where the subject fall a sleep very quickly.(see figure from Lagarde [4]).

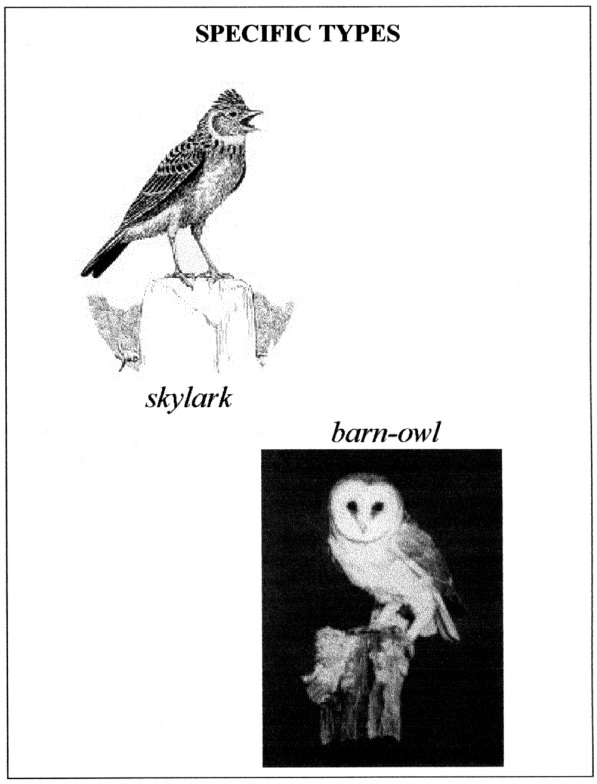


On an other hand a lot of parameters called psychophysiological concomitants are linked to the evolution of the vigilance curve . The most important parameter is the cognitive and physical performance. The subject will be very performant during the hypervigilance periods and less performant during the hypovigilance periods. If a soldier would like to optimize his performance , he has to respect this physiological data : is a physiological requirement.

Each subject need a determined number of sleep hours . Some need 5 hours per day , others need 10 hours and the majority of people need between 7 and 8 hours of sleep. The repartition of sleep hours during the nycthemera is like a Gauss curve (see figure).[5]



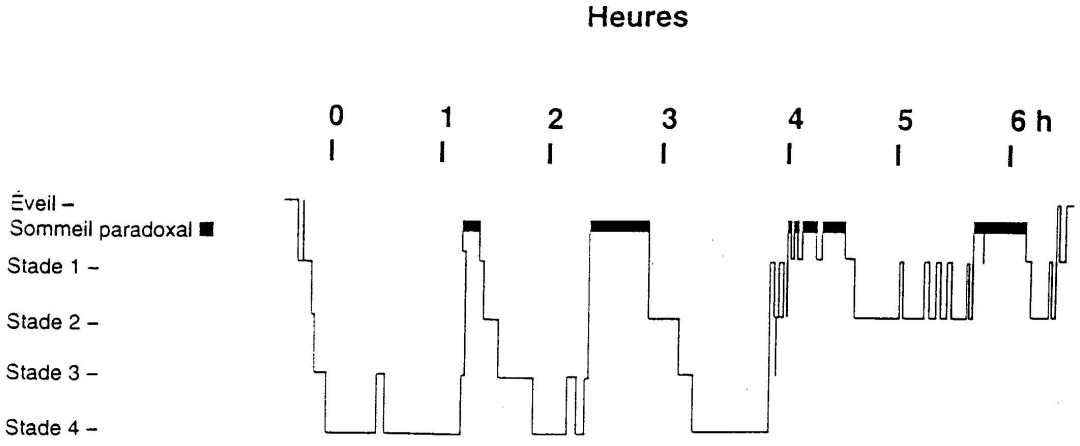
An other sleep characteristic is the fact that some people are very efficient early in the morning , others are better late in the evening . The first one are called « skylark » type , the second « barn-owl » type (see picture). A specific scale from Horne and Ostberg is used to determine the specific type of the sleep of a subject.[6].



Since the possibility to record the electric activity of the brain (Hans Berger 1929) , a lot of treatment of the EEG (electroencephalogram) signal have been made ; one of the most important is those use by Rechtshaffen and Kales who edited in 1968 a manual for standardized terminology , techniques and scoring system for sleep stages of human subjects [7].With this scoring system is possible to individualize one stage of wakefulness and five stages of sleep :

Stage 1 or drowsiness stage belong to the slow light sleep
Stage 2 is the slow light sleep
Stages 3 and 4 are the slow deep sleep
Stage 5 or REM sleep (Rapid Eye Movement) is called the paradoxical sleep.

The quantitative importance of each stages is not equal : stage 1 represent only 5% of the total sleep stages , stage 2 : 50% , stages 3 and 4 : 25% and REM sleep : 20% .
The qualitative importance is also very different : the stage 1 is just an intermediate stage between wakefulness and sleep ; the stage 2 is like a buffer very useful during sleep deprivation by protection of the slow deep sleep ; the stages 3 and 4 seem to be important in the physical recovery period ; the REM sleep is involved in the memory process.
It is usual to represent a night by a special figure called an hypnogram (see figure)



Hypnogram of a normal night

Each individual has his own sleep characteristics , which move during the life , but that exist from the birth , may be they are genetics.
Is quite impossible to modify these characteristics ; for example is possible to reduce the sleep duration from 8 hours to 5 hours , but a sleep debt appear and the next night you have to sleep more than 8 hours to compensate a part of the sleep debt.

So , is easy to understand that a sleep disturbance (sleep deprivation , a fractionated night , …) induce a modification of the efficiency of the subject in a negative way.

SUSOPS AND CONOPS

The recent events as Golfe war or Kosovo conflict or the future missions which will be devoluted to the European Rapid Reaction Force will be included in two types of operations : the sustained operations (SUSOPS) and the continuous operations (CONOPS).
A physiological definition of these operations put in evidence the role played by the rest and specially a good management of sleep periods.

A SUSOPS is a military operation characterized by a conflict of very high intensity , limited in the time (one or few days) but with no possibility to sleep.
A CONOPS is a military operation characterized by a conflict of relatively low intensity , on a very long period (many weeks or months) , with a possibility to sleep but not every time during the night and not during a recovery period of eight hours.

In both cases , these type of operations induce fatigue , sometime due to jet-lag , to sleep loss , to the intense physical activity , to the stress , and sometimes due to a combination of all these parameters.
As it was indicated in a technical note written for the US soldiers involved in the Yugoslavia conflict [8]: « whenever soldiers are moved quickly from one part of the world to another , several days are required to adjust to new conditions . Upon arrival , body rhythms function as if they were still on home station time zones . Soldiers may have trouble sleeping when they would normally be awake , especially if several time zones have been crossed . Soldiers with jet lag may be sleepy during the day , have degraded mental performance and difficulty sleeping at night. Their biological clocks will gradually adjust in response to local sunrise and sunset ; although the process of adjustment generally takes four to seven days if soldiers do not prepare in advance . Soldiers do more work and perform better when they are rested . Mental or cognitive performance is affected by sleep loss earlier than physical performance . Sleepy soldiers do not always think clearly , plan effectively or follow procedures correctly. A 25% decline in effectiveness can be expected for every 24 hours without sleep. Performance on monotonous or repetitive tasks is degraded first. Symptoms of sleep loss include extreme sleepiness , lapses in attention, irritability , lack of initiative , susceptibility to accidents and decrease attention to self-care. All soldiers are affected by sleep loss , but leaders and command/control personnel who deal with many cognitive task and complex decision making are most vulnerable. Soldiers who are well rested are less susceptible to disease and heal more quickly. »
All the symptoms will be detailed in a next conference , but it is an evidence that there is an antinomy between the physiological requirements and the operational requirements , which induce fatigue with a decrease in efficiency and security.
The management of sleep-wakefulness during SUSOPS and CONOPS seems to be a necessity to maintain the capability of the soldier and to give an optimal security to himself and to the crew from which he belong.

SCIENTIFIC PROGRAM

The goal of the lectures indicated below is to inform all military personnel (medical and command or headquarters) about the physiological requirements of the sleep-wakefulness cycle , the vulnerability induced by the opposition between physiological and operational requirements , and the possibilities to manage as well as possible the vigilance , keeping in mind at the same level the efficiency and the security of the subject.
In a first time we will see the individual differences observed in the population and the effects of sleep deprivation and jet lag which are the major reasons of the symptoms observed. We will see after the physiological measures to counteract the fatigue : i.e. the napping strategy and the influence of some parameters on the level of vigilance like food , exercise etc…Then we will approach the difficult question of the pharmacology :wakening substances , sleep inducing substances and chronobiotic substances. To conclude , a round table with all speakers and the audience will try to clarify the ethic problem , the self-medication ,…At least some practical recommendations will be given.

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Individual Differences in Vigilance and Performance during Continuous/Sustained Operations

Maria Casagrande
Dipartimento di Psicologia
Università degli Studi di Roma "La Sapienza"
Via dei Marsi, 78 – 00185 Roma, Italy

Aeronautica Militare Italiana, CSV, Reparto Medicina Aerospaziale, Pratica di Mare, Pomezia (Roma)

ABSTRACT

Military operations are often characterised by prolonged periods of wakefulness; irregular rest-activity patterns; long haul flights. These situations are unnatural. Severe sleep debt can accumulate, leading to dangerous levels of sleepiness and decreases of performance. Although sleep deprivation, time of day and time on task are considered among the most important causal factors of daytime sleepiness, the levels of vigilance may still significantly vary according to individual differences. Verifying whether and to what extent some stable individual differences are associated to specific variations of vigilance and performance may be important in orienting the best criteria for the selection of personnel involved in prolonged activity for many hours or unusual hours, and/or monotonous activity.

Concerning individual differences, a distinction can be made between the so-called temporary individual differences and permanent individual differences. The former are to be considered as a series of coping mechanisms, i.e. the set of capacities and abilities that modify workloads or directly affect the homeostatic and/or circadian factors that induce sleepiness. These are considered as the outcome of an active sphere of behaviour which makes individuals directly "involved" in handling their own activities. Permanent differences, instead, are to be considered as "constitutional" differences, i.e. as characteristics that exist for genetic and/or physiological reasons, including gender, age, some personality features (such as extroversion/introversion, field-dependence, etc.) and circadian typology. Some individual coping strategies can minimize the adverse effects of sleep loss and circadian rhythm desynchronization and promote optimal vigilance and performance in operational settings. Equally, some individual traits can facilitate a good adaptability to continuous/sustained operations. Both an age less than 40-50 years and morningness are particularly crucial deteminants of a good adaptability to work at unusual hours and, maybe, to continuous/sustained operations. Equally, both flexibility of sleeping habits and ability to overcome drowsiness are related to both better long-term tolerance in shiftwork and the capacity to sustain vigilance and performance at unusual hours and over time. Studies on other individual traits have given more inconsistent results. Even though it is possible to outline which individual traits are likely to allow better adaptability to continuous/sustained operations, our understanding of the mechanisms involved is still not very clear and definitive. In fact, poor attention has been paid to such important factors as individual ones. There is a surprising lack of studies on individual differences in the adaptability to continuous/sustained operations. Many factors have contributed to this condition. Studies on individual differences are necessarily long, time consuming and require a large sample size. If we can overcome these limitations, then it will be possible to choose the best criteria for the selection of personnel involved in continuous/sustained operations, and also to identify those who run the greater risk of a fall in vigilance and of performance errors in order to adopt the necessary preventive measures.

INTRODUCTION

Military operations are often characterized by prolonged periods of wakefulness, irregular rest-activity patterns and long haul flights. These situations are unnatural. Severe sleep debt can accumulate, leading to dangerous levels of sleepiness, performance decreases and a reduced margin of safety. These factors can increase vulnerability to accidents in operational settings. Although sleep deprivation, time of day and time on task are considered among the most important causal factors of daytime sleepiness (e.g. Åkerstedt and Kecklund, 1994), the levels of vigilance may still significantly vary according to individual differences. Some

Paper produced for the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

individual characteristics contribute, in fact, in modulating general levels and time of day effects of vigilance, sleepiness and performance, and even modulate the intensity with which the various deactivating factors act individually (e.g. Åkerstedt and Torsvall, 1981; Harma, 1993). Verifying whether and to what extent some stable individual differences are associated to specific variations of vigilance and performance may be important in orienting the best criteria for the selection of personnel involved in prolonged activity for many hours or unusual hours, and/or monotonous activity.

The first thing to consider when dealing with the problem of individual differences concerns the distinction made between the so-called *temporary* individual differences and *permanent* individual differences (Harma, 1993). The former are to be considered as a series of coping mechanisms, i.e. the set of capacities and abilities that modify workloads or directly affect the homeostatic and/or circadian factors that induce sleepiness. These are considered as the outcome of an active sphere of behavior, which makes individuals directly "involved" in handling their own activities. Permanent differences, instead, are to be considered as "constitutional" differences, i.e. as characteristics that exist for genetic and/or physiological reasons, including gender, age, some personality features (such as extroversion/introversion, field-dependence, etc.) and circadian typology.

Temporary individual differences or coping mechanisms

Coping strategies for sustaining vigilance and performance during continuous/sustained operations

Coping strategies (or styles) play a major role in an individual's physical and psychological well-being when he or she is confronted with negative or stressful life events (Endler and Parker, 1990). In early research, coping was conceptualized as an unconscious process. In more recent research, however, coping has been considered as a response to external stressful or negative events (e.g. McCrae, 1984). These responses are usually conscious strategies or styles on the part of the individual. Furthermore, some individuals may have particular coping styles in responding to different stressful situations (Carver et al., 1989). Coping behaviours have been categorized into three major coping styles: a) responses that change the situation, b) responses that change the meaning or the appraisal of the stress, and c) responses aimed at controlling distressful feelings (Endler and Parker, 1990). Sustaining vigilance and performance during prolonged periods of wakefulness, continuous operations and/or at unusual hours is a stressful situation; therefore, if people adopt adequate coping strategies, they will be able to reduce the adverse factors affecting continuous/sustained operations and/or shiftwork tolerance.

Coping with the stress of working unusual hours

Commitment to work for many hours or unusual hours may be one of the most important individual factors affecting continuous/sustained operations and/or shiftwork tolerance (Harma, 1993). Depending on the "commitment", several coping mechanisms may be promoting adjustment to work at unusual hours or for a prolonged period. In fact, a good "commitment" allows people to schedule their lives, and especially their sleeping habits (e.g. Monk and Folkard, 1985). For example, people may be able to sleep more before coming to work, take naps during rest periods and adopt adequate eating regimens and physical activity (Rosa, 1990). Good commitment is also affected by financial rewards or by other incentives such as time off and work advancement (Barton 1994; Minors and Waterhouse, 1983).

In short, good "commitment" may be an important factor allowing a good management of vigilance, reducing sleep debt - and therefore sleepiness - during shiftwork and continuous/sustained operations.

Health and physical fitness

Shiftwork and continuous/sustained operations are associated with several acute and chronic health problems, most of which are related to a disarray of circadian rhythms. These health disorders can be greater in people with medical complaints. A less positive attitude to shiftwork has been observed among workers reporting impaired subjective health when compared to those perceiving themselves as relatively healthy (Dirkx, 1987). Negative correlations between attitudes towards shiftwork and the frequency of complaints about chronic fatigue, cardiovascular and psychoneurotic symptoms, and sleep complaints after night shifts have been found. Specifically, it has been suggested that people suffering with digestive tract diseases or sleep disorders should be excluded from job schedules leading to work at unusual hours (Rutenfranz, 1982).

On the other hand, physical fitness is a factor increasing tolerance to working unusual hours (Hanna, 1993). In a series of studies, it was shown that physically-fit subjects reported lower levels of general fatigue and an

increase in sleep length (Harma, 1993). In addition, in one epidemiological study, physical exercise was rated as the most important daily factor promoting sleep and improving its quality (Urponen et al., 1988). Physical fitness thus seems to decrease sleepiness, probably due to improved sleep. In addition, different studies have reported that the rhythm amplitudes of physically-fit subjects are higher than in unfit individuals (Atkinson et al., 1993; Harma et al., 1982). Since individuals with a high amplitude in their circadian rhythms have been found to be more tolerant to shift work, physically-fit subjects should be more tolerant to shiftwork (Reinberg et al., 1988). It is thought that large amplitudes result in a greater stability of circadian rhythms and that this is beneficial in coping with frequent rhythm disturbance (Atkinson et al., 1993).

Flexibility of sleeping habits

Many studies have shown that sleepiness presents a bi-modal distribution with a night-time peak and one in the early hours of the afternoon, defined by Lavie (1986) respectively as “primary and secondary sleep gates”. Times of day effects of sleepiness are evident, above all, when the sleep-wake cycle is organized in very short cycles (e.g. 7 min of sleep and 13 of wakefulness). In this case, sleepiness increases during the night showing a trend characterized by two superimposed components: a slow component, which follows a linear circadian trend, and an ultradian quick component. Even vigilance follows a bi-modal distribution that occurs with a strong decrease of sleepiness in a daytime period between 10.00 and 11.00 and in a nighttime period between 21.00 and 23.00, defined by Lavie (1986) as “forbidden zones for sleep”. Probably due to high or low levels of rigidity of this circadian and ultradian organization of vigilance, there are subjects who are able to sleep only at specific times. Other individuals seem to have some additional physiological processes, namely “sleep ability” and “wakeability”, that allow them to sleep and wake up easily at different times. In other words, the “rigidity-flexibility” in the circadian organization of the sleep-wake cycle might allow a “rigidity-flexibility” of sleeping habits. Based on Folkard and coworkers’ (1979) definition, “flexibility of sleeping habits” quantifies the self-reported rigidity in sleeping habits. This individual characteristic should help people to sleep when it is possible and not only when there are the best circadian conditions. Thus, flexibility of sleeping habits should be related to a greater ability to sustain continuous operations and to work at unusual hours, As a matter of the fact, flexibility of sleeping habits is related to better long-term tolerance to shiftwork (e.g. Costa et al., 1989; Iskra-Golek, 1993).

Ability to overcome drowsiness

“Ability to overcome drowsiness” defines the ease with which individuals can overcome drowsiness (Folkard et al., 1979). This factor, too, is related to better long-term tolerance to shiftwork (e.g. Costa et al., 1989; Iskra-Golek, 1993). Furthermore, Vidacek et al. (1987) showed that “ability to overcome drowsiness” was the best indicator of shiftwork tolerance after three years of shiftwork. Like “flexibility of sleeping habits”, even this factor seems to be related to characteristics of circadian organization of vigilance, but, unlike the former, it also seems affected by individual coping strategies, In fact, overcoming drowsiness would be facilitated in those subjects who are able to grasp every strategy useful to sustain vigilance and to reduce sleep deprivation. Thus, people with high adaptability to shiftwork and to continuous/sustained operations should be able to: take naps when possible; have appropriate timings of exposure to environmental or bright artificial light; adopt good eating and drinking regimens; do adequate physical exercises.

Napping behavior

Many laboratory studies have documented that napping has positive effects on alertness in various settings (Lumley et al., 1986; Bonnet, 1991; Dinges, 1992; Bonnet et al., 1995; Gillberg et al., 1996; Horne and Reyner, 1996; Reyner and Horne, 1997; Hayashi et al., 1999a, 1999b). In particular, the restorative effects of a short nap (20-30 min) were observed after a normal night’s sleep (Hayashi et al., 1999a; 1999b), after a restricted night’s sleep (Gillberg et al., 1996; Home and Reyner, 1996; Reyner and Horne, 1997), during 64 hours of continuous work (Naitoh et al., 1992) in young adults, and after a normal night’s sleep in the elderly (Ceolim and Menna-Barreto, 2000).

Individual differences in napping behavior allow distinguishing between nappers and non-nappers. Based on an extensive review on napping behavior, Dinges (1992) reported that on average 61% of adults nap at least once a week. Napping more than once within a day is extremely rare. The duration of naps is about 73 minutes; no study found nap duration of <15 min or >120 min to be common.

According to several studies (Evans et al., 1977; Dinges, 1992), naps are taken for the following two reasons: 1) replacement naps, taken in response to a sleep debt, and 2) appetitive naps, taken without regard to sleep

debt, as a result of an endogenous biphasic sleep-wake cycle. In fact, in the regular nappers, there were subjects who reported napping only when tired (subjects defined by Dinges as *replacement or compensatory nappers*); while other subjects reported napping even when not tired, and hence were called *appetitive nappers*. Appetitive nappers appear to be adapted to getting sleep; they not only nap frequently without shortened sleep the night before, but they also report being able to fall asleep almost anywhere, and they do not have to be tired to nap. Since both prophylactic and compensatory napping behaviors are beneficial for reducing sleep loss and for improving performance during continuous/sustained operations, individual differences in napping behavior might be relevant for selecting personnel adapted to sustained prolonged periods of wakefulness.

Coping strategies for improving environmental conditions

Improving the environmental conditions leads to bettering the conditions of workers during continuous/sustained operations. Further, several environmental factors can increase alertness, enhance performance and can partially counter the effects of sleep loss (Penn and Bootzin, 1990). Thus, when environmental conditions are monotonous and not very arousing and when the demands of the task allow it, workers involved in continuous/sustained operations should be able to adopt strategies to improve vigilance, enhance morale and prevent performance decrements over time.

Auditory stimulation: sounds and music as environmental arousers

Meaningful and unpredictable sounds, such as speech, traffic noise and music, generally increase vigilance and improve performance (Davies and Tune, 1969). Noise is not always found to be beneficial, however. Noise produces a decrease in performance if it is loud enough to mask feedback from instruments or inner speech (Poulton, 1977), or if task demands are heavy (Loeb and Alluisi, 1977). Usually, music leads to a higher performance than the one found with noise (Penn and Bootzin, 1990). In addition, music presented on a random schedule increases performance more than continuous music or music presented at a fixed interval (Davies and Parasuraman, 1982). Penn and Bootzin (1990) concluded that background music or other meaningful auditory stimulation played at moderate levels could increase performance, prevent performance decrements over time and enhance morale. Music that is lively and varied is the most arousing,

Bright light

Bright light treatment can be used in managing the physiological mechanisms associated with sleepiness. Exposure to bright light during the night shift can induce physiological adaptation to night shift work and also improve daytime sleep (Czeiler, Jhonson, Duffy, Brown, Ronda, Kronauer, 1990). Exposure to bright light during the night can directly enhance alertness (Badia, Myers, Boecker, Culpepper, 1991) and an increase in vigilance and performance has been found after repeated brief (10 min) green light exposures during the night (Horne, Donlon, Arendt, 1991). Many experimental and some field data suggest that the use of bright light can be very useful for improving alertness and performance during nighttime work and continuous operations.

Ambient temperature

High ambient temperature can be considered as a stressful event. Thus, during continuous/sustained operations and shiftwork it may be appropriate to maintain a constant and moderate temperature (Bonnet, 1990; Lagarde e Batejat, 1995).

Eating and drinking regimen

During continuous/sustained operations workers frequently consume food and drink during breaks. This consumption produces direct effects on arousal. Summing up, light to moderate amounts of high protein foods may help to sustain arousal and high carbohydrate foods may produce sleepiness (e.g. Lennernans, Ambræus e Åkerstedt, 1994; Tepas, 1990). As everybody knows, caffeine has a stimulant effect (e.g. Gillin, 1994). Caffeine is found not only in coffee but also in tea, chocolate, and Coca-Cola. Caffeine may be used effectively as a stimulant to combat sleepiness. Individuals differ in their response to caffeine, with some people being overstimulated. Others are less affected, especially chronic users who appear to develop some tolerance to the stimulating effect of caffeine. Further, an indiscriminate use of caffeine may lead to deleterious effects on sleep (Gillin, 1994). Daytime ingestion of alcohol may promote sleepiness and a small amount of alcohol it often used to induce sleep propensity. Although low-to-moderate amounts of alcohol initially promote sleep by shortening sleep latency and reducing wakefulness for 3 to 4 hours of the night, it often disrupts and fragments sleep during the latter half of the night (Gillin, 1994).

Sleep hygiene

Many deleterious effects of continuous/sustained operations are the result of sleep deprivation. Thus, proper information on factors that affect sleep is very important in order to adopt adequate coping strategies. Sleep hygiene includes information on the effects of sleep loss, sleep scheduling, circadian rhythms, naps, sleep habits, caffeine, cigarette smoking, alcohol, ambient temperature, environmental light and environmental noise on sleep (Penn and Bootzin, 1990). Zarcone (1,994) proposed some rules for obtaining good sleep, which are adapted for people with regular night sleep opportunity. It should also be useful to propose general rules in order to facilitate proper sleep in workers involved in continuous/sustained operations.

Permanent or constitutional individual differences

Circadian rhythm desynchronization

Most behavioral and physiological processes are characterized by a temporal structure that matches the 24-h day-night cycle. The most salient behavioral marker circadian rhythmic output in human adults is the daily sleep-wake cycle. A similar 24-h time frame constrains a myriad of functions, including endocrine secretions, body temperature regulation, gastrointestinal functions, sensory processing and cognitive performance (e.g. Moore-Ede et al., 1982). Many of these rhythms are usually synchronized. Prolonged periods of wakefulness, irregular rest-activity patterns, and working for many hours and/or at unusual hours, leads to a transient and repeated misalignment of circadian rhythms. During the circadian realignment process there are three mechanisms by which mood, well-being and performance efficiency can be adversely affected. First, sleep will be disrupted and the individual will be in a state of partial sleep deprivation. Second, the new time of wakefulness is likely to tap into the “down phases” of various psychological functions that are normally coincident with sleep in the day-oriented individual. Third, the various individual components of the circadian system will be in a state of disarray, with the normal harmony of appropriate phase relationships destroyed (e.g. Åkerstedt et al., 1989). Following on from this, working at unusual hours can cause sleepiness, gastrointestinal symptoms and a decrease in performance. Circadian adjustment is slow. In addition, fast circadian adjustment may be beneficial only in slowly rotating shift systems, while in rapidly rotating shift schedules, fast circadian adjustment may be unnecessary and even detrimental. Depending on the coping strategies adopted – and also perhaps on some physiological traits – strong individual differences in the amount of circadian rhythm desynchronization can be evident. As a matter of fact, desynchronization of circadian rhythms of body temperature and sleep-wakefulness has been found in a majority of subjects with poor tolerance to shiftwork (e.g. Reinberg et al., 1989).

“Sleepy” and “Alert” subjects

Studies using very short sleep-wake cycles (e.g. 7 min of sleep and 13 of wakefulness) (Lavie, 1992) or subjective measures of sleepiness, as *Epworth Sleepiness Scale* (Johns, 1991a) allow distinguishing between “sleepy” and “alert” subjects.

The *Epworth Sleepiness Scale* (ESS) (Johns, 1991 a) is a brief self-administered questionnaire which asks subject to rate, on a scale of 0-3, the chances that in recent times he/she would have dozed in eight specific situations of daily life, that are more or less soporific. The subject is required to retrospectively evaluate part of his/her usual behaviour and to distinguish dozing behaviour from feelings of tiredness. This very simple method for evaluating daytime sleepiness seems to reflect a steady individual trait; in fact, test retest administrations show that paired ESS scores do not change significantly and are highly correlated (Johns, 1991b). In patients suffering from sleep disorders, ESS scores are correlated with mean sleep onset latencies measured in a *Multiple Sleep Latency Test* (MSLT). Finally, the ESS scores significantly distinguish normal subjects from several groups of patients with sleep disorders characterised by different levels of daytime sleepiness (Johns, 1991b). A study considering two groups of college students with low (alert subjects) and high (sleepy subjects) ESS scores showed that sleepy subjects, as compared to alert subjects, evaluated themselves as more sleepy, had more episodes of daytime sleepiness, presented a greater number of naps and their naps had a longer duration (Casagrande, Violani, Testa, Curcio, 1997). In addition, sleepy subjects had the worst performance on a Letter Cancellation Task with respect to alert subjects (Casagrande, Violani, Curcio, Bertini M, 1997)

The reliability and validity of the ESS, the rapid completion time, test length and ease of self-administration make it a useful measure for evaluating daytime sleepiness as a persistent individual trait. Sleepy subjects complain of high levels of daytime sleepiness, can easily fall asleep when instructed to do so, but also fall

asleep when instructed to remain awake; finally, they need a greater amount of sleep. Alert subjects, on the other hand, do not complain of daytime sleepiness, cannot easily fall asleep when instructed to do so, but can easily remain awake; finally, compared to sleepy subjects, they need less sleep (Lavie, 1992). Due to these individual differences along the sleepy-alert continuum, alert subjects seem to be more suitable for sustaining continuous operations.

Morning types and evening types

Kleitman (1963) was the first investigator to propose the existence of morning and evening type subjects, whose body temperature and efficiency curves peaked at different times during the sleep-wake cycle. Individual differences in chronotypology have been investigated by means of questionnaires. Oquist (1970) formulated a questionnaire in order to classify subjects on the basis of their self-assessed preference for time of day. He described Morning-types (M-types), Intermediate or Neither types (N-types) and Evening types (E-types). Horne and Hostberg (1976) produced a new version of this questionnaire: the Morningness-Eveningness Questionnaire (MEQ). It consists of 19 questions on individual rising and bedtimes, preferred times for physical and mental activity, and subjective alertness. The questionnaire has been standardized in various countries. The use of the MEQ in research into biological rhythm has provided significant results. There is general agreement that morning persons reach their peak body temperature and diurnal efficiency, 2-3 hrs earlier than evening persons (e.g. Horne et al., 1980; Foret et al., 1982). With regard to sleep habits, M-types have earlier bed times and rising times than E-types (e.g. Froberg, 1977; Kerkhof, 1985). With respect to the sleep-wake cycle, M and E-types differ in phase position, regularity and flexibility, and E-types have a more flexible sleep-wake cycle than morning type persons (e.g., Foret et al., 1982; Kerkhof, 1985; Ishihara et al., 1987).

Vidacek et al (1988) found a phase-advance difference of nearly four hours in morning types. Ishihara et al (1987) found that, except for REM latency, which was shorter in morning types, there were no differences in the polysomnographically recorded sleep parameters; but, other authors (Foret et al., 1985; Kerkhof, 1991) failed to replicate this finding. Lavie and Segal (1989) evaluated differences in the structure of daytime sleepiness. Nocturnal sleep efficiency was higher in morning than in evening types. After sleep deprivation, evening types slept more during the morning period, whereas a mid-afternoon peak in sleepiness was not found in this group. Evening types were sleepier during the morning but, on the whole, suffered less from daytime sleepiness and had a better performance on a Letter Cancellation Task with respect to morning type subjects (Casagrande, Violani, Curcio, Bertini, 1997). On the other hand, Froberg (1977) found no significant differences between M and E-types in letter cancelling, maze learning, syllogism and numerical vigilance, measured 3-hourly during 75 h of sleep deprivation. Åkerstedt and Froberg (1976) reported no M-E type differences in an auditory addition and attention test given five times over one day. Patkai (1971) measured performance with the Stroop test, arithmetic ability and reaction time at three times over a day. Significant M-E type differences were found only for the latter task. Horne et al (1980) reported significant differences between M and E-types in the number of items correctly rejected in a line inspection task. M-types' correct rejection levels were significantly better than E-types' in the morning, whereas they were worse during the evening. Whilst E-types showed a steady improvement throughout the day, M-types showed a general decline. A post-lunch dip in performance was quite evident for M-types, but not for E-types. In addition, the circadian trends in correct rejection levels and body temperature were highly positively correlated for E-types, but a significant negative relationship between these parameters was found for M-types.

In a review of findings on morningness and eveningness, Kerkhof (1985) concluded that morning types exhibited a relatively advanced phase position of their sleep-wake behavior, subjective alertness and body temperature when compared to evening types. In addition, on the basis of the less intraindividual variability of sleep times, the smaller numbers of nocturnal awakenings, the higher sleep quality and the lower frequency of naps during morning hours, Volk et al (1994) suggested a stronger synchronization of the sleep-wake cycle in morning types.

The difference in circadian phase position between M and E types is believed to influence their different adaptability and tolerance to night-work, with M-types being less tolerant (e.g. Breithaupt et al., 1978). Conversely, Costa et al (1989) found that morningness appeared to be unrelated to long term tolerance, but did influence circadian adjustment and sleep behavior. M-types showed less delay in their circadian phase-position and less of an adjustment in their sleeping times. In addition, Costa et al. (1989) found that subjects with digestive disorders showed a greater phase shift and a reduction in amplitude on night work, suggesting a possible relationship also between short-term circadian adjustment and long-term tolerance to shiftwork.

Some studies attempt to relate individual differences in Morningness with Eysenck's personality dimensions. There are studies which find a correlation between morningness and extraversion but not between morningness and neuroticism: M-types tending to be more introverted than E-types (e.g., Folkard et al., 1979; Ishihara et al., 1987; Wilson, 1990).

Introversion and extroversion

According to Eysenck's (1967) theory, large numbers of empirical investigations find three major dimensions of personality: extraversion-introversion (E-I), neuroticism-stability, and psychoticism-superego. These three dimensions appear to be relatively immune to cultural factors and have a strong genetic basis, which suggests that there must be some psychological, anatomical or biochemical-hormonal factors underlying the observed behavior patterns. Eysenck's first explanation of E-I was in terms of excitation-inhibition balance. In extraverts, hypothetical inhibitory potentials would develop rapidly and dissipate slowly. Later, the theory of E-I was reformulated in terms of the arousal concept. Individual differences in E-I would be associated with states of arousal in the cortex, mediated probably by the reticular formation. Compared to extraverts, introverts are hypothesized to be more cortically aroused. In addition, there is thought to be an inverted U arousal-performance relationship. In monotonous situations, introverts would sustain their attention better than extraverts, but factors changing levels of arousal (noise, time of day and so on) could reverse performance trends. Eysenck has also suggested a link between vigilance and arousal. Arousal facilitates the maintenance of attention over time; hence, introverts do better than extraverts. Several extensions of Eysenck's theory have been introduced. Humphreys and Revelle (1984) explained task performance in terms of both arousal, considered as resource availability, and effort, considered as resource allocation. Hockey (1986) proposed that introverts have more internal control over their activity than extraverts, with the consequence that the performance of introverts is affected much less than that of extraverts by manipulation of arousers (such as noise, incentives and so on). M.W. Eysenck (1988) suggested that introverts differ from extraverts in arousability rather than in basal levels of arousal.

On the other side of the physiological characteristics of the I-E dimension, what is the relationship between the E-I dimension, on the one hand, and vigilance and performance, on the other? There are contrasting experimental results with regard to this issue. Blake and Corcoran (1972) found that introverted subjects had better performance than extroverts in the morning, whilst they showed a steady decrease in performance throughout the day. Some studies reported a possible relationship between the I-E dimension and tolerance to shiftwork (Blake and Corcoran, 1972; Colquhoun and Folkard, 1978; Iskra-Golek, 1993). Extroverted subjects should be more tolerant to shiftwork than introverts, whereas introverts had better performance and suffered less frequently from drowsiness. After considering 56 experiments on the relationship between E-I and vigilance/performance, Koelega (1992) found that 40 (70%) of them fail to show a difference in favour of introverts in the overall performance level. The main finding of a meta-analysis showed that: many studies have failed to support E-I differences in vigilance tasks; more E-I differences are found in visual tasks than in auditory tasks and in studies using extreme introverts and extraverts; when extreme introverts and extraverts are considered, introverts are superior in absolute levels of detection but not in maintaining detection efficiency over time (Koelega, 1992).

Neuroticism

Neuroticism-stability is one of the dimensions of Eysenck's (1967) theory. According to Eysenck's (1967) theory, individual differences in neuroticism are associated with the limbic system and differences in psychoticism are associated with androgen hormones.

Subjects with higher scores on neuroticism had a faster performance on a visual search task and evaluated themselves as more tired (Casagrande, Violani, Curcio, Bertini, 1997). Colquhoun and Folkard (1978) found that "neurotic-extrovert" subjects show the greatest degree of adjustment of their body temperature rhythms to phase shifts; while Nachreiner (1975) pointed out that more introverted and emotionally unstable subjects are less tolerant to shiftwork.

Field dependence

Some studies (Sarmany, 1984) attempted to relate vigilance and sleep with individual differences in cognitive style, such as those hypothesized by the field-dependence personality theory. Witkin and co-workers (Witkin, Dyk, Faterson, Goodenough and Karp, 1962) proposed that individuals differ along the field dependence-independence continuum. According to the field-dependence theory, characteristics of field-independent

individuals include: a) a high degree of analytical ability, that is, the capacity to separate the relevant from the irrelevant (vs. a more global style); b) an active and objective approach (vs. a passive and subjective approach); c) a relatively greater control of impulses and mood (vs. greater impulsivity); d) less manifest anxiety; e) a more well-defined sense of identity, as well as more self-confidence. In addition, field-dependent individuals should be more arousers and thus they should be less sleepy than field-independent subjects. There are contrasting experimental results on this issue. Some studies found that field-dependent individuals have higher levels of vigilance and a better performance (Natale, 1997; Rhodewalt and O'Keeffe, 1986), whereas others found that field-dependent subjects as compared to field-independent subjects were less sleepy only in the morning (Casagrande, Violani, Curcio, Bertini, 1997), and had a worst performance (Casagrande, Violani, Curcio, Bertini, 1997; Marincola and Long, 1985).

Age

Age is one of the major predictors of sleep length and sleep quality in connection to the night shift. It is suggested that proneness to internal desynchronization of the circadian system increases with age, making it more susceptible to a disturbance of the sleep-wake pattern (Åkerstedt and Torsvall, 1981). It appears that at around 45 years of age, difficulties in connection with the night shift start to increase with increased exposure to the night shift. The reason for the negative effects of experience are unclear, but one might think that decreased circadian flexibility could be involved and that more time for recuperation with increasing age causes an accumulation of negative effects (Åkerstedt and Torsvall, 1981; Foret et al., 1982). In addition, there is evidence to suggest that people become more M-type as they get older. Thus, morningness might also play a role in explaining some of the problems that the late middle-aged and elderly have in coping with shiftwork (Monk, 1990).

Gender

In a study investigating the differences between male and female shiftworkers, Oginska et al. (1993) found that men slept more than women and that women experienced more sleep disturbances than men and suffered more frequently from drowsiness during work. It would be difficult to judge whether an insufficient amount of sleep in case of shiftworking women and their drowsiness at work should be considered as relating to a biological-based greater need for sleep; it might rather be the result of the double burden of female workers: the job and family. However, studies comparing male and female workers with a similar workload have not found differences between genders in shiftwork tolerance (e.g. Olsson et al., 1990). Women generally suffered more than men from symptoms considered as specific to the "intolerance syndrome", i.e. psychoneurotic, digestive and circulatory symptoms, and those of chronic fatigue. However, after 40-50 years their subjective health generally improved, whereas in males one observed the consequent deterioration of health with advancing age.

CONCLUSIONS

In industrialized societies, there are an increasing number of situations (i.e. continuous work in essential services and in high responsibility tasks) that require sustained operations during which irregular rest-activity patterns are needed. The attempt to sleep and to work at unusual hours (to sleep during the day and to work during the night), with respect to the underlying circadian rhythm, often causes loss and/or changes in the structure of sleep and increased sleepiness. If, as normally happens during intense military operations, it becomes necessary to prolong irregular rest-activity patterns for some days in stressful situations, a severe sleep debt and circadian rhythm disruption can accumulate. Both of these physiological factors lead to increased sleepiness, decreased performance and reduced margin of safety on the job. All of these factors increase vulnerability to accidents and mistakes in operational settings.

Alertness management strategies can minimize the adverse effects of sleep loss and circadian rhythm desynchronization and promote optimal vigilance and performance in operational settings. No single strategy can fully counteract the sleepiness and performance decrements typically recorded during night shifts and continuous operations. A combination of strategies may provide the greatest potential to optimize alertness and performance in operational settings. To improve performance and to effectively contrast the adverse interactions of the aforementioned factors, one possibility is to use short periods of "prophylactic sleep" (before long periods of work) or to take naps during the work period (Nicholson 1986). Other useful strategies could be: multiple napping regimens; bright light treatment; adopting behaviors encouraging health and

physical fitness; promoting coping strategies to improve both flexibility of sleeping habits and the ability to overcome drowsiness; training people to adapt coping strategies for improving environmental conditions. The levels of vigilance may also significantly vary according to individual differences. Some individual traits contribute, in fact, in modulating general levels and time of day effects of vigilance.

According to studies on interindividual differences, it might be concluded that there are some people who suffer very little from working at unusual hours or for prolonged periods, while others find it almost intolerable. A number of authors have shown that age and morningness-eveningness are particularly crucial determinants of a good adaptability to work at unusual hours and, maybe, to continuous/sustained operations. Some authors have shown that extreme M-types suffer more from shiftwork and prolonged periods of wakefulness than E-types subjects. The reason for this difference may include the reduced susceptibility to physical zeitgebers shown by E-types and the difficulties that morning types have in sleeping late during the morning. Although individual traits should remain constant throughout life, there is evidence to suggest that people become more “M-type” as they get older. Thus, morningness might also play a role in explaining some of the problems that the late middle-aged and elderly have in coping with working at unusual hours (Monk, 1990). Equally, both flexibility of sleeping habits and the ability to overcome drowsiness are related to both better long-term tolerance in shiftwork and the capacity to sustain vigilance and performance at unusual hours and over time. Studies on other individual traits have given more inconsistent results. Although some approaches appear very productive, much more work needs to be done in order to have accurate reliable results on this topic.

Even though it is possible to outline which individual traits are likely to allow better adaptability to continuous/sustained operations, our understanding of the mechanisms involved is still not very clear and definitive. In fact, poor attention has been paid to such important factors as individual ones. Most studies on individual differences have considered vigilance and performance during night shifts or have focused on shiftwork tolerance. Very few studies have considered individual differences in the management of sleep loss or have considered sleep deprivation tolerance. Furthermore, there is a surprising lack of studies on individual differences in the adaptability to continuous/sustained operations. Many factors have contributed to this condition. Studies on individual differences are necessarily long, time consuming and require a large sample size.

To find out which individual characteristics can guarantee the best adaptability to sustained operations and to irregular or unusual rest-activity schedules, it is essential to define: a) which physiological, behavioral and/or psychological parameters are useful for defining the “adaptability dimension"; b) which individual traits can allow us to predict adequate adaptability. To evaluate both the “adaptability construct” and “individual traits”, it is necessary to take into account a very large number of variables: psychological, subjective, behavioral, physiological/biological, psychophysiological, and chronobiological. It is also necessary to use a multivariate statistical approach, which necessarily calls for very large samples of subjects (it is estimated that about 12 observations are needed for each considered variable). If we can overcome these limitations, then it will be possible to choose the best criteria for the selection of personnel involved in continuous/sustained operations, and also to identify those who run the greater risk of a fall in vigilance and of performance errors in order to adopt the necessary preventive measures.

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An Overview of Sleep Deprivation and The Ameliorative Effects of Modafinil

Ross A. Pigeau
Defence and Civil Institute of Environmental medicine
1133 Sheppard Ave, W., P.O. Box 2000, Toronto, Ontario, Canada M3M 3B9

Executive Summary

The objective of this paper is to examine total sleep deprivation in the context of its behavioral and cognitive effects, as well as to look at some of the ways these effects can be minimized. The paper is presented in two parts: in the first, a general introduction to sleep deprivation is given, examining subjective and objective measures of fatigue, and its effects on performance, including the influence of fatigue modifiers. The second part looks at a new pharmaceutical substance known as modafinil that appears to reduce sleepiness by inhibiting naturally occurring sleep mechanisms.

The distinction between sleepiness and fatigue is highlighted, with both conditions affected by a number of modifier variables each of which can interact with the other to exaggerate or moderate performance decrements due to sleep loss. The term sleepiness is used to describe the pressure to fall asleep that is associated with circadian rhythms. The term fatigue, on the other hand, is used for the diminishing ability of the pre-frontal cortex. to function while suffering from sleep loss.

The military needs to understand how best to cope with the effects of sleep deprivation. While scenarios involving total sleep deprivation combined with continuous cognitive work are not common, when they do occur the accompanying loss in performance (30% after one night and 60% after the second night) can be unacceptably high. Without opportunities for taking a nap, often the only alternative solution for remaining alert (at least in the short term) is stimulants. In this context, understanding the potential of the new drug modafinil is crucial, as it may offer a safer alternative to the more commonly used substance amphetamine.

One of the notable possible side effects of Modafinil discussed in this paper is the overconfidence effect, where subjects fail to realize that their own performance levels have decreased. The effect is discussed in terms of the difference between sleepiness and fatigue. It is suggested that modafinil, unlike amphetamine which is a general central nervous system stimulant, inhibits the experience of sleepiness without similarly ameliorating pre-frontal cortex fatigue. Until the requisite studies are performed to test this hypothesis, it is suggested that modafinil be used with caution for tasks requiring high-level cognition during sleep deprivation. Nevertheless, the relatively benign pharmacological properties of modafinil do make it a safe and worthy alternative to amphetamine for counteracting the effects of sleep loss.

Abstract

An overview of total sleep deprivation is offered that attempts to sample the broad array of studies conducted in the area. A distinction is made between sleepiness and fatigue as explanations for the behavioural effects attributed to sleep loss. The first, sleepiness, concerns itself with the pressure to fall asleep that is moderated by circadian pressures, while the second, fatigue, addresses a hypothesized monotonic (more or less) degradation in capability in the pre-frontal cortex. It is shown that both effects can be influenced by a number of modifier variables each of which can interact with each other to exaggerate or moderate cognitive declines due to sleep loss. The second part of the paper discusses a new pharmaceutical substance known a modafinil and its ability to ameliorate sleep deprivation effects. It is suggested that modafinil may be beneficial for counteracting sleepiness, but that it may not be as successful for counteracting fatigue effects, suggesting that modafinil should be used with caution for tasks requiring high-level cognition.

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

> *…there are times when even having an interesting and challenging task to do isn't enough to keep my reactions from slowing to the pace of molasses or to maintain my motivation to perform. It is this last sensation that I find most disconcerting. I've worked through fatigue before – as a university student, I did my share of all-night cramming, and as a journalist, I often worked long hours with little sleep – but still, I'm disturbed by the loss of will to persevere that accompanies my extreme sleep-deprived state.*
>
> *I can't help wondering what would happen if I were called upon now to perform tasks or make decisions with life-or-death consequences.*
>
> -- Asleep in the Fast Lane: The impact of sleep on work, Dotto, [36], p.6

For those who have endured it, sleep deprivation can be a humbling experience. It can rob us of our intellectual abilities, our coordination and our motivation. Even highly trained and motivated individuals can succumb to sleep loss-induced fatigue (Pigeau et al, [91]) and fatigue due to sleep loss has been implicated in many automobile accidents [40, 44, 77, 90, 107]. Indeed, it is likely that few of us have reached adulthood without having experienced at least one night of sleep loss: e.g., while caring for a sick child, cramming for exams, travelling to distant lands, performing shift work, enjoying celebrations, etc.

But what can be said of sleep deprivation other than it causes fatigue? To say that one gets tired when sleep deprived may be accurate, but is it profound? For instance, what is the nature of fatigue? How is the fatigue associated with physical exertion different from that of sleep loss? What are the behavioural manifestations of fatigue and when do they become dangerous? Are all aspects of human performance equally susceptible to fatigue? Does sleep loss affect behaviour directly or do more primary effects on motivation and emotion mediate it? Is there a linear relationship between amount of sleep loss and amount of fatigue? Is sleep the only remedy for fatigue? If so, how much sleep is necessary? If not, what are the safe alternatives? Can fatigue even be measured or can it only be inferred from its effects on other measurable behaviours? Is there a difference between fatigue and sleepiness?

The purpose of this paper is to explore some (but not all) of these questions. It will broadly survey the literature on sleep deprivation as well as illustrate some of the findings from sleep loss studies performed in our laboratory. The goal is to give an appreciation for the general phenomenon of sleep deprivation, one that examines its known principles while attempting to impart the richness and complexity of many of its enduring mysteries. Part One gives a general introduction to sleep deprivation proper, and Part Two explores one of the ways sleepiness due to sleep loss can be ameliorated using a new pharmaceutical substance known as modafinil.

Part One: Overview of Sleep Deprivation

Sleep deprivation is the condition where an organism is deprived of sleep either acutely or chronically for a period longer than the normal wake/sleep circadian cycle – i.e., roughly longer than 16 hrs awake if we assume that 8 hrs of sleep per 24 hr day is normal. For the purposes of this paper we will consider only total sleep deprivation; that is, periods of continuous sleep loss without intervening naps. Although total sleep deprivation occurs relatively infrequently in society (except perhaps for military operations) the effects are important for serving "as a comparison to improve understanding of the effects of partial sleep loss and sleep disruption" (Walsh, p.73 [106]).

As the word *deprivation* implies, to go without sleep is to go without a necessary condition for normal human functioning. Although there is still some question as to the exact purpose of sleep in humans [10, 33, 57, 63, 68], it is a common observation that going without sleep precipitates feelings of sleepiness and fatigue that, in turn, can have secondary negative consequences on performance and behaviour. Much sleep deprivation research has concerned itself with exploring these secondary negative consequences[1].

[1] We ignore *positive* consequences of sleep deprivation, such as its therapeutic effect for clinical depression or its ability to lower seizure thresholds, because these consequences, though important, are relatively rare in the general population.

However, before surveying the performance consequences of sleep deprivation it is first important to establish the validity of the claim that the primary consequence of sleep loss is indeed fatigue and sleepiness. Otherwise, the inference that performance suffers as a result of fatigue due to sleep deprivation is put into question. How then are sleepiness and fatigue measured?

Measuring sleepiness and fatigue.

There are essentially only two ways of measuring levels of fatigue and sleepiness: the first, which are called subjective methods, are limited to humans, and the second, which are called objective methods, are applicable to most of the higher organisms. The subjective method is predicated on the assumption that humans are capable of monitoring their own psychological state (e.g., positive and negative mood) and, further, that they are capable of articulating the status of that state (e.g., respond to questionnaires). The objective method is predicated on the assumption that the phenomenon of 'sleep' itself is measurable and, further, that the propensity for falling asleep is a direct indication of level of sleepiness. Although fatigue and sleepiness are often used interchangeably, they are not necessarily the same phenomenon. As we will see, the measurement of fatigue is more problematic than the measurement of sleepiness.

SUBJECTIVE MEASURES.

The first and most obvious method for estimating the level of fatigue and sleepiness resulting from sleep loss, at least in humans, is to ask them. The Stanford Sleepiness Scale [55], the U.S. Air Force School of Aerospace Medicine (SAM) Subjective Fatigue Checklist [47], the Profile of Mood States [82], and the Profile of Fatigue-Related Symptoms [99] are all examples of methods for quantifying fatigue and sleepiness based on an individual's ability to evaluate their own subjective state. Ignoring the interesting psychological question of *how* humans are able to do this – i.e., how are humans capable of doing *any* meta-level task (e.g., thinking about thinking)? – employing questionnaires to measure levels of fatigue and sleepiness have been widely used in sleep deprivation research.

Figure 1 illustrates mean responses for both the Stanford Sleepiness Scale and the SAM fatigue checklist from subjects undergoing a 64 hrs sleep deprivation drug study. Subjects worked continuously on a large battery of tasks with only 15 minutes of rest (without sleep) between successive 1 hour and 45 minutes work sessions. The results are taken from the placebo group who completed the questionnaires each hour throughout the sleep loss period. Notice that subjective levels of sleepiness and fatigue increase over the 64 hours of sleep loss but that the increase is not monotonic – i.e., it varies with time of day (more on this effect later). Notice also that although subjective assessments for 'sleepiness' and 'fatigue' are derived from different questionnaires – the Stanford Sleepiness scale is based on a single response to a seven point descriptive scale, and the SAM fatigue checklist is based on responses to 10 items none of which mentions sleepiness – the plots for sleepiness and fatigue are almost identical. The correlation between them is in fact 0.96. This finding questions either the substantive difference between the concepts of fatigue and sleepiness or the ability of subjects to distinguish them experientially.

Despite this difficulty in distinguishing between fatigue and sleepiness, subjective measures are important for establishing the *face* validity of the concepts. They are important for meaningfully grounding fatigue and sleepiness in personal experience. Indeed, much of the performance-based research in sleep deprivation (to be discussed later) would be weakened if it had not already been established that subjects do in fact experience fatigue and sleepiness, and more importantly can report its effects consistently. Without this most basic of first steps, the interpretive significance of attributing performance degradations to fatigue or sleepiness would be in doubt. Subjective measures, however, although necessary, are rarely sufficient for exploring psychological constructs fully. It is also necessary to measure constructs more objectively, without resorting to the human ability to meta-cognize about their own condition.

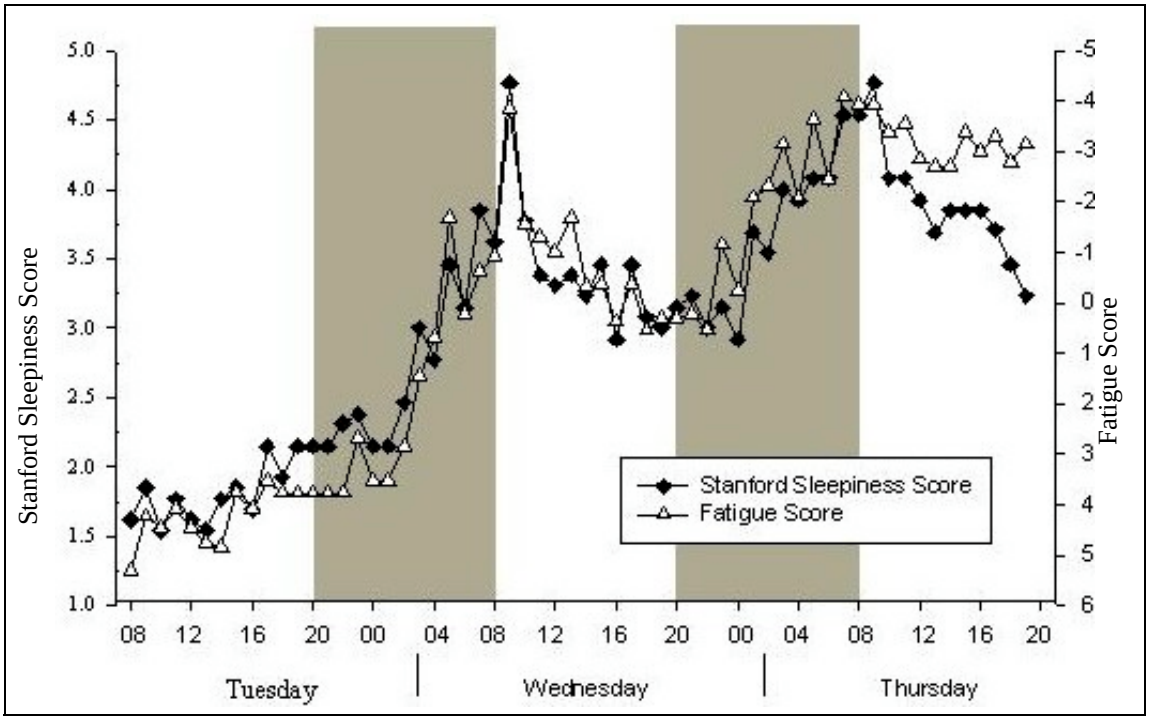

Figure 1: SAM Fatigue and Stanford Sleepiness Scales

OBJECTIVE MEASURES.

Since sleep deprivation is, of course, about loss of sleep then it should be possible to infer sleepiness from the propensity to fall asleep given the opportunity. This is the logic behind the Multiple Sleep Latency Test (MSLT) [27, 29] where subjects are asked to lay down in a dark, quiet room and to try to fall asleep. The test lasts 20 minutes, and the time it takes for subjects to fall asleep (if they do) is meant to reflect level of sleepiness. For instance, if someone falls asleep within 10 minutes of closing their eyes he or she is considered more 'sleepy' or 'tired' then if it takes 15 minutes. The MSLT is based on two assumptions. First, it is based on the assumption that normal humans are incapable of falling asleep at will (especially if well rested). If they could then the inference that sleep onset time reflects sleep propensity (or sleepiness) would be invalid. Second, it assumes that an objective method for determining sleep onset exists. Fortunately, such a method has been found in brain electroencephalography (EEG). Sleep EEG is a well-established and repeatable pattern of brain electrical activity. By connecting head mounted electrodes to specially designed filters and amplifiers, cortical electrical activity can be measured whose frequency and amplitude fluctuate in time. Using a procedure standardized by Rechtschaffen and Kales [100] sleep can be categorized (and scored) into different stages – stages that reflect relatively unique patterns of electrical activity and that reflect depth of sleep (e.g., see Niedermeyer [89]). With EEG indicators of sleep onset, the MSLT has been shown to be a good indicator of sleep propensity with very short sleep onset times occurring during extended periods of sleep deprivation [28, 29].

A problem with the MSLT, however, is that it can take as long as 20 minutes to administer the test (if subjects are well rested). In sleep deprivation studies that require continuous cognitive work (e.g., [1, 53, 92]), allowing subjects multiple opportunities to rest can compromise the experimental paradigm. In military operations, for example, the only reason personnel would be deprived of sleep for long periods is because they need to perform critical tasks. Therefore the MSLT is inappropriate for Sustained Operations (SUSOPs) studies – i.e., studies designed to investigate the effect of continuous cognitive work during total sleep deprivation.

An alternative to the MSLT is the Maintenance of Wakefulness Test (MWT) proposed by Mitler, Gujavarty and Browman [85]. Instead of asking subjects to try to fall asleep while lying in a bed, the MWT requires them to try to stay awake while sitting in a chair. The MWT was originally developed to assess excessive somnolence such as that found in narcolepsy and has been used to study stimulants for its treatment (e.g., see Mitler [86]). Unfortunately, the MWT, like the MSLT, also takes 20 minutes to administer. Independently of Mitler et al. [85], Pigeau, Heslegrave and Angus [94] and Pigeau, Angus and

Heslegrave [93] developed a version of the MWT suitable for total sleep deprivation studies. During every hour of a 46 hrs sleep deprivation experiment, while working continuously on a battery of 30 cognitive tasks and questionnaires (except for a 15 min break every two hours), the subjects were required to relax in their chairs with their eyes closed but to try to remain awake. After 4 minutes (subjects were unaware of the duration) the computer terminal beeped loudly, they opened their eyes, responded to a brief drowsiness questionnaire and then continued with the next task in the battery. The EEGs during these 4 minutes eyes closed periods were scored for sleep onset latency as well as for amount of time spent asleep. The results of these analyses are shown in Figures 2A and B, and clearly show the effects of sleep deprivation. Sleep onset latency decreased and time spent asleep increased with increasing sleep loss, with both graphs showing modulations due to circadian influences. Notice that Figures 2A and B have two plots each. One represents 4 min eyes closed sessions occurring immediately after the 15 min break, and the other represents 4 min eyes closed sessions occurring 1 hour into the work period. There is clearly a 'break' effect where subjects show reduced propensity for sleep (i.e., less sleepiness) immediately after their break versus 1 hour into the session. Though less obvious, this effect is also present in Figure 1 where a small saw-toothed oscillation is noticeable in the subjective estimates. The implication of this break effect will be discussed later in the section entitled 'Effects on Performance'.

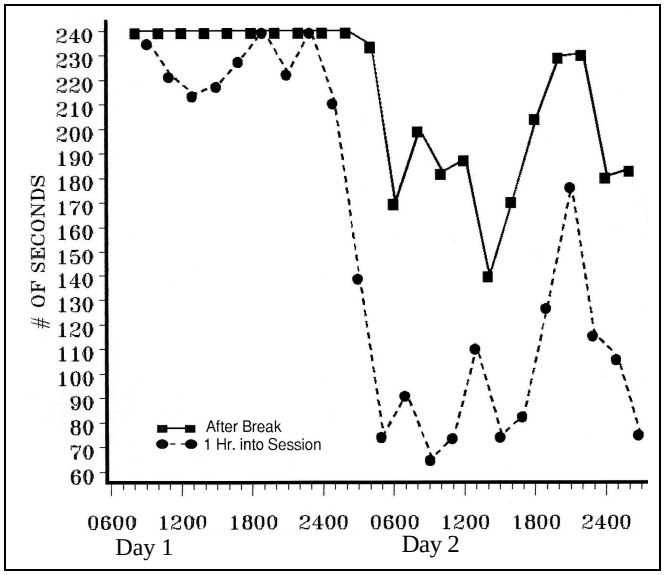

Figure 2A: Sleep onset latencies during the 4 minutes eyes closed task.

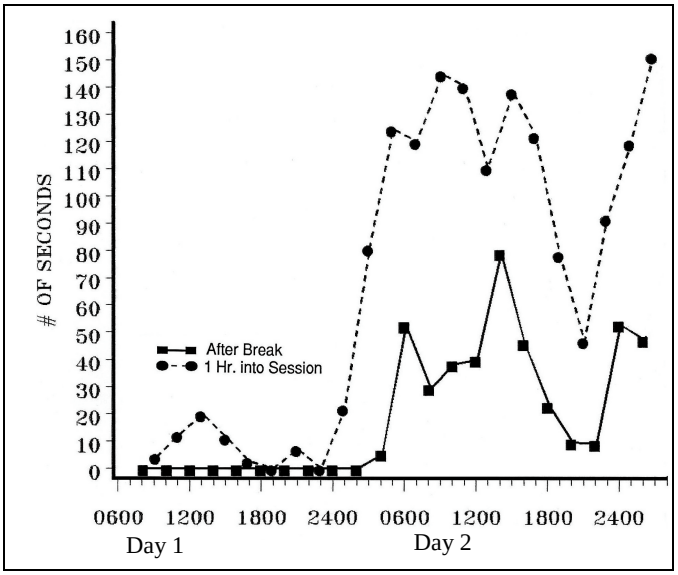

Figure 2B: Total sleep time during the 4 minutes eyes closed task.

The value of having objective measures of sleepiness, especially electrophysiological ones, is the possibility for exploring sleep onset using more sophisticated analytical techniques. The results illustrated in Figure 2 were generated laboriously by hand scoring paper printouts from each subject's EEG for each 4 min eyes closed session throughout the sleep deprivation period. Alternatively, the electrical signals from the cortex can be digitised at suitably fast sampling rates and saved on a computer. A host of very powerful signal processing techniques are then available to analyse the waveforms (e.g., Fast Fourier Transforms (FFTs), period analysis, autocorrelations, coherence analysis, etc.). Figure 3 illustrates one such analysis, performed on the EEG signal from a single subject during four progressively later 4 min eyes closed sessions. Each 3-dimensional graph represents a power frequency spectrum of brain electrical activity from .5 to 25 cycles per second (Hz) – .5 Hz is on the right side of the graph progressing to 25 Hz is on the left side. Time flows from back to front and covers a single 4 min eyes closed session. Figure 3A represents a 4 min session occurring only 5 hours into a sleep deprivation period when the subject is alert. Notice the 'mountain range' of Alpha activity (8-12 Hz) throughout the 4 min period. Alpha activity occurs predominantly when a subject's eyes are closed and they are resting; but they remain alert and awake. Alpha attenuation is one of the first signs of falling asleep and it is clearly evident in Figure 3B after 25 hours of wakefulness. A burst of Alpha activity at the beginning of the 4 min session indicates the subject initially closes his eyes, but the peak disappears quickly, within 30 seconds, as the subject falls

asleep. Notice the increase in slow frequency activity (Theta 4-8 Hz and Delta .5-4 Hz), also an indication of sleep. By chance, before the end of the 4 minutes, the subject awakens spontaneously and produces a burst of Alpha activity again. Figure 3C is interesting because it documents the struggle to remain awake after 31 hours of sleep deprivation. Three episodes of sleep onset are clearly visible with the overall power of each alpha burst steadily decreasing throughout the 4 min period. Finally, Figure 3D shows the subject at 03:00 hrs after 45 hours of sleep deprivation. He falls asleep within 7 seconds of closing his eyes and remains asleep for the full 4 minutes. As the high amount of slow frequency activity would suggest, the subject was later scored as being in late stage 2 or early stage 3 sleep by the end of the session – a stage that would take 20 or more minutes to reach during a regular night's sleep.

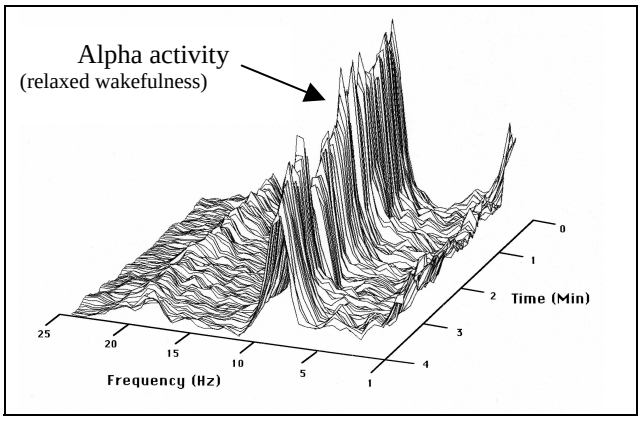

Figure 3A: 5 Hrs Awake

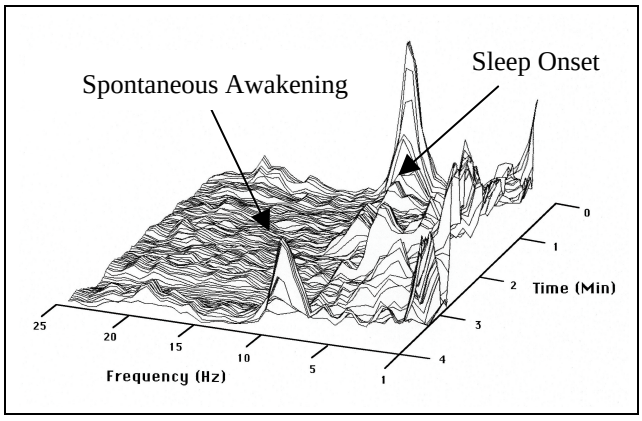

Figure 3B: 25 Hrs Awake

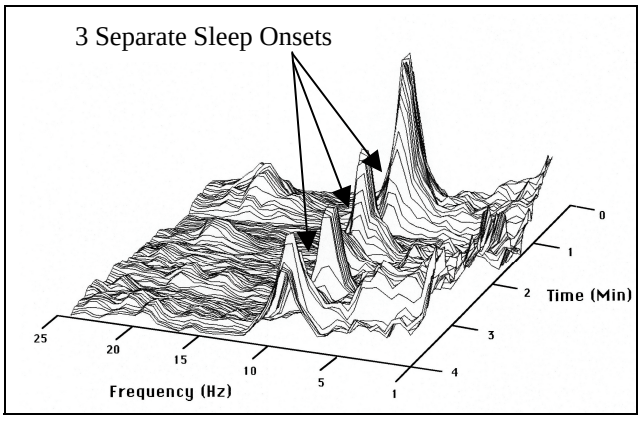

Figure 3C: 31 Hrs Awake

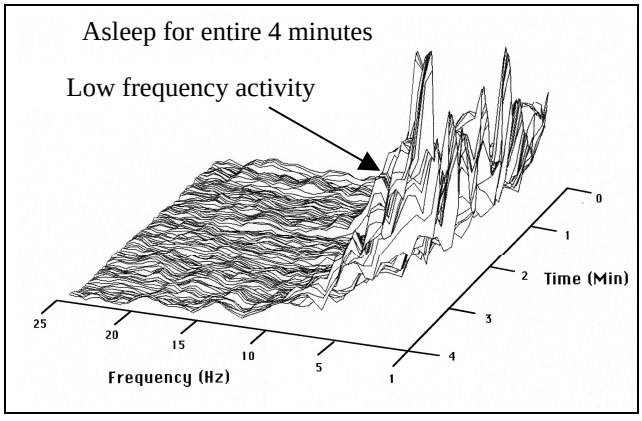

Figure 3D: 45 Hrs Awake

The advantage of digitising EEG goes well beyond the ability to display pictures of sleep onset, however. By calculating estimates of Alpha, Theta and Delta, a composite measure of sleepiness (or drowsiness) can be calculated for each 4 min session for each subject, yielding an EEG derived index of sleep propensity (see [93, 94]). Figure 4 plots the mean EEG derived drowsiness index for 9 subjects calculated from frequency analysed brain electrical activity for the 4 min eyes closed sessions. The equation used to derived the EEG index was: $\left(\frac{A}{Ab}\right) - \left(\frac{T + D}{Tb + Db}\right) + 1$ where A, T and D refer to Alpha, Theta and Delta activity generated during the 4 min sessions, and Ab, Tb and Db are constants derived from baseline levels of Alpha, Theta and Delta for each subject when they were fresh and alert. Pigeau, Angus and Heslegrave [93] found that the EEG derived drowsiness index had a mean multiple correlation of 0.63 with subjective measures of fatigue and sleepiness, and was a good alternative estimate of sleep propensity that did not require manual sleep stage scoring.

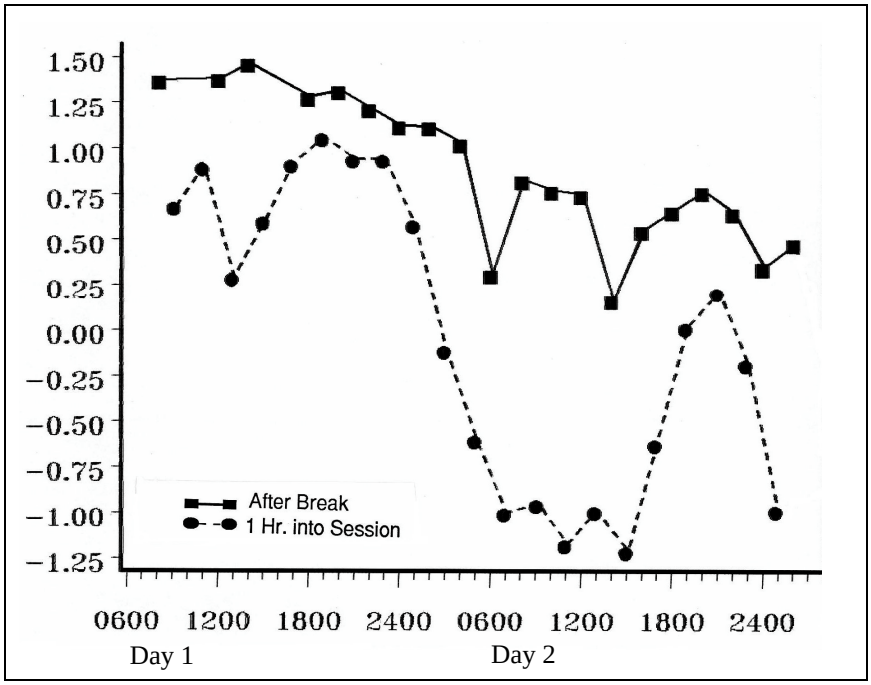

Figure 4: EEG Drowsiness Index

The discussion thus far has concentrated on objective measures of sleepiness derived from EEG indices of sleep. Lorenzo, Ramos, et al. [79], Cajochen, Brunner, et al. [24] and Corsi-Cabrera, Arce, et al. [32] have shown that the absolute power of EEG (i.e., the sum of Alpha, Theta, Delta and Beta power) during wakefulness also increases with increasing sleep deprivation. These results are consistent with the early work of Naitoh, Pasnau and Kollar, [87]. The increase in EEG power during wakefulness suggests that cortical neurons (the source of brain electrical activity) are firing more synchronously, which in turn suggests less cortical differentiation. A similar result was found by Jeong, Kim, Kim et al. [61] using an entirely different approach. Using non-linear mathematical techniques they found that the dimensional complexity of cortical EEG is lower after sleep deprivation than before, suggesting a lowering in the information processing capability of the brain. In contrast to the results of studies that estimate sleepiness by measuring the propensity to fall asleep, these studies on waking EEG suggest that the brain may be suffering from a more global and generalized form of fatigue. These studies suggest that there may be more at stake in sleep deprivation than simply increased pressure towards sleepiness – that, in fact, fatigue and sleepiness may be different phenomena with fatigue being a homeostatic process and sleepiness being a circadian process.

If fatigue and sleepiness are not the same then why are the plots for subjective fatigue and subjective sleepiness almost identical in Figure 1? Shouldn't one (fatigue) reflect a more monotonic increase as time awake increases and thus reflect decreasing levels of cortical differentiation, while the other (sleepiness) show more circadian variability to reflect the basic sleep/waking cycle (as seen in core temperature data, for instance [65])? The fact that subjective fatigue and sleepiness show similar patterns may have two explanations. First, it is possible that questionnaires of subjective fatigue and sleepiness are not sensitive enough to differentiate the concepts. But implicit in this explanation is the assumption that subjects could in fact tell the difference between fatigue and sleepiness if they were asked the right questions. Yet would not the ability to make such fine semantic discriminations also be susceptible to sleep deprivation, therefore confounding cause and effect? The second explanation is equally problematic. If fatigue were indeed associated with a generalized decrease in cortical differentiation, and sleepiness was similarly associated with (presumably) sub-cortical circadian pressures for sleep, both processes would nonetheless reside in, and have effects upon, the same brain – the brain that subjects must use to make their subjective assessments. Subjects, therefore, may be incapable of distinguishing between fatigue and sleepiness not because the questions in questionnaires are poorly chosen, but because the (hypothesized) brain mechanisms responsible for fatigue and sleepiness have a generalized effect on the very organ that subjects must use to interpret the questions to begin with.

There are techniques for extracting monotonic versus circadian trends in sleep deprivation data, for example linear regression, fast Fourier transforms, autocorrelation and consinor analysis. One of these, complex demodulation [101, 104], has a number of benefits the most valuable of which is the reconstruction of the original waveform using the best fitting frequency model. Figure 5 illustrates the results of a complex demodulation performed on the Stanford Sleepiness data presented in Figure 1. Note both the linear component and the circadian (i.e., 1 cycle per day) reconstruction of the raw data, which account for approximately 95% of the variance. When complex demodulation is used to decompose behavioural data in sleep deprivation studies (see the next section for examples) some authors (e.g., [3, 39]) use the term fatigue to "represent the mechanism responsible for the monotonic trends of performance decrement seen during sleep deprivation, that is, the amount of prior wakefulness" (Babkoff et al. p.419 [3]). They view sleepiness as related to non-task variables that can have both monotonic and rhythmic components. Other authors, however, in deriving models of sleep regulation, consider the monotonic trend associated with increasing sleep deprivation as a homeostatic process indicating the "propensity for sleep initiation" ([19], p.150; [18, 20]) – seen in Figure 5 as a negative exponential curve rather than as a straight line. In other words, they interpret it as sleepiness.

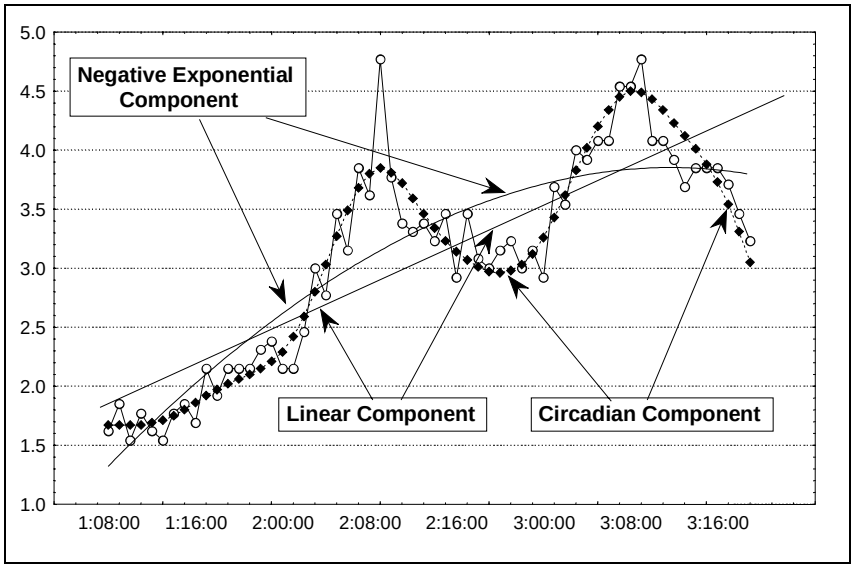

Figure 5: Results of Complex Demodulation on Stanford Sleepiness Scores

This brief review of the measures of fatigue and sleepiness demonstrates that the concepts are not nearly as obvious as they may first appear. On the one hand, it is clear that sleep deprivation induces greater propensity to fall asleep. This is consistent with both subjective reports and with EEG analyses of sleep onset. On the other hand, the role that *fatigue* plays in sleep loss is more ambiguous. It seems confounded with sleepiness using either subjective or objective methods for measuring it. As we will see in the next section, however, it may be possible to infer fatigue from its effects on performance.

Effects on Performance

If sleep deprivation resulted in only minor decrements in performance there would be little reason to study it. As the opening quote by Dotto [36] for this paper suggests, sleep deprivation can have substantial effects, particularly on mood and performance. For example, Angus and Heslegrave [1] found that when sleep deprivation was coupled with continuous cognitive work "large decrements occurred during the first night of sleep loss (reductions of about 30%), with performance becoming generally unacceptable during the second night (about 60% reductions)" (p.66). They found similar affects on mood. Plot A in Figures 6 and 7 demonstrate the considerable drop in performance for a serial reaction task (SRT) and a logical reasoning task (LRT) during a 64 hours sleep deprivation/continuous work study [92]. The placebo group in that study suffered a 28% (SRT) or a 32% (LRT) decline in the number of correct responses per minute after 24 hours of wakefulness, followed by a 57% (SRT) or a 53% (LRT) decline after 48 hours.

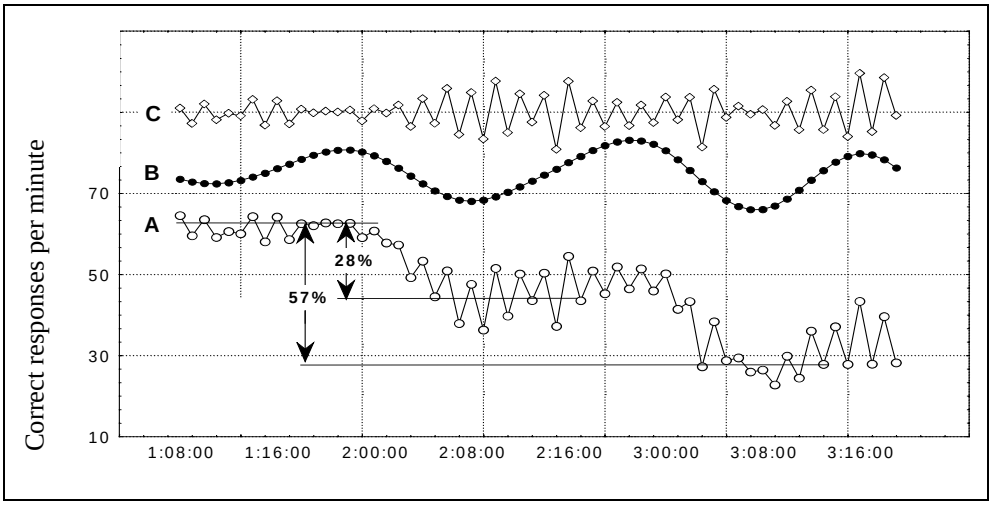

Figure 6 : Serial Reaction Time

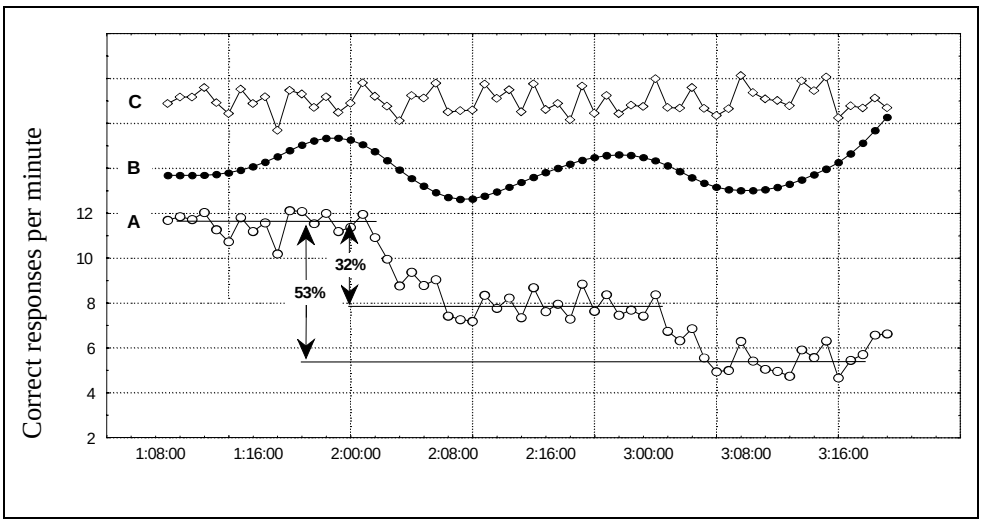

Figure 7: Logical Reasoning Task

In a meta-analytical study, Pilcher and Huffcutt [97] quantitatively analysed the results of 19 sleep deprivation experiments and reported that mood and cognitive performance were strongly impaired by sleep loss:

> Our results confirm that sleep deprivation has a significant effect on human functioning. By quantitatively combining across primary studies, we found that the mean level of functioning of sleep-deprived subjects was comparable to that of only the 9th percentile non-sleep-deprived subjects… (p.323)

Although the finding that sleep deprivation adversely affects performance is now well accepted in the literature (e.g., see [51, 62, 67]), there is still debate over the robustness of the effects, the circumstances under which they occur and the causal mechanisms behind them. For example, Wilkinson [108], in noting how motivation can counteract the effects of sleep loss, has commented that "the adverse effects of sleep deprivation on performance and behavior are very labile and can easily be cancelled by suitably arousing conditions" (p.255). As it turns out, there are many modifying variables for exacerbating or moderating the effects of sleep deprivation – motivation is but one of them. We will review these modifying variables and then briefly introduce the two main theories developed to explain the effects on performance.

FATIGUE MODIFIERS.

In his 1982 review Johnson [62] introduced three categories or classes of variables that influence the direction and the magnitude of effects on performance during sleep deprivation. Not surprisingly, the first and most important of these classes of variables is level of fatigue, which Johnson equates with the amount of prior wakefulness[2]. Amount of prior wakefulness is *the defining* variable for sleep deprivation experiments. Without it there would be no field of investigation. As a result, amount of prior wakefulness is almost invariably used as an independent variable (i.e., a manipulated variable) in sleep loss studies.

The manner in which amount of prior wakefulness affects performance, however, will depend upon Johnson's next two classes of variables: 1) task and 2) non-task variables (see Figure 8). As the name implies, task variables are those aspects of a task that will influence or modify the task's sensitivity to sleep deprivation. Johnson specifies seven task variables: complexity (e.g., number of mental operations), difficulty, duration, knowledge of results (i.e., feedback), memory requirements, pacing (e.g., self vs. work paced), and proficiency level (i.e., novice vs. well trained).

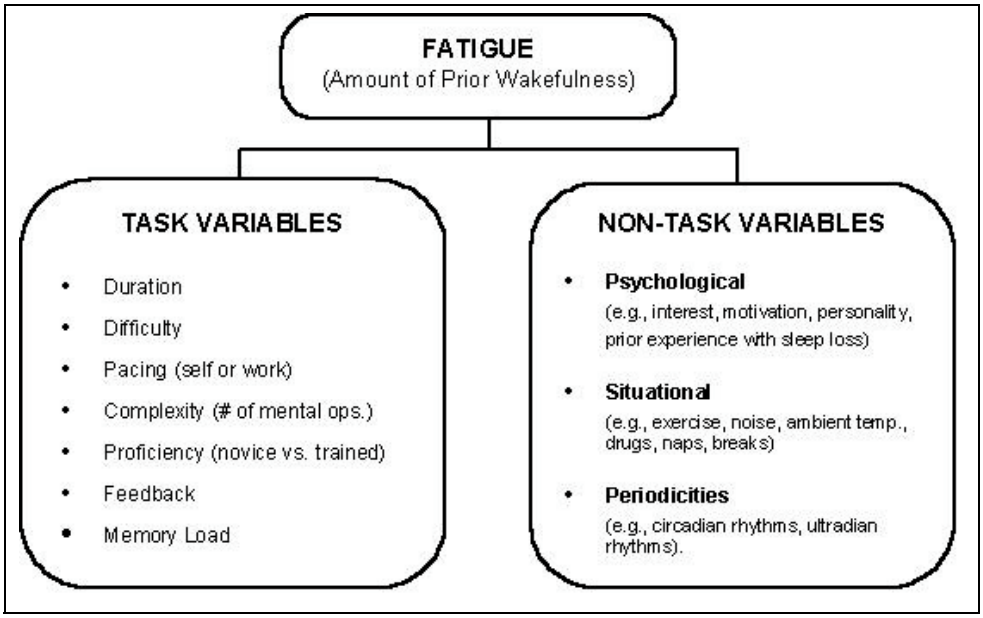

Figure 8: Johnson's (1982) 3 classes of modifying variables

The duration of vigilance tasks has long been known to interact with sleep loss [108]. Modest periods of wakefulness (e.g., 24 hrs) require longer task durations to demonstrate effects on performance whereas longer periods of sleep deprivation (e.g., >48hrs) yield performance decrements for much shorter task durations [35, 109][3]. Another example of a modifying task variable is complexity. Vigilance tasks are known for their dull and monotonous nature, but if they are replaced with tasks of greater complexity the effects of sleep loss can be much reduced, presumably due to their arousal inducing value (e.g., Harrison [51]). Table 1 presents Johnson's list of seven task variables along with their hypothesized impact on performance during sleep deprivation. As can be seen from Table 1, to maximize the possibility of detecting sleep loss effects tasks should be long, difficult, boring (i.e., have low complexity), provide little or no feedback, entail high memory requirements, are work paced and should be performed by novices. It is this combination of task characteristics that prompted Wilkinson [108] to conclude, "sleep deprivation reduces the non-specific arousal level of the body, but has no specific effects" (p.254). But as we will see in the next section, this conclusion may be incorrect. Sleep deprivation may have very specific effects, particularly on tasks requiring the pre-frontal cortex.

Non-task variables are Johnson's third class of modifiers affecting performance during sleep loss. Non-task variables are divided into three general sub-classes: psychological, situational and rhythmical variables. Psychological variables include interest, motivation, age, personality type and prior experience

[2] But as we have discussed in the previous section, the distinction between fatigue and sleepiness is not entirely clear, and this confusion will have implications for theories attempting to explain performance loss (more on this later).

[3] Although a more recent study by Gillberg and Akerstedt [46] casts doubt on the ubiquity of this effect.

with sleep loss. Horne and Pettitt [56] have shown that monetary rewards for good performance maintained baseline levels for 36 hrs without sleep, but that this incentive was only moderately successful after the second day. More significantly, they showed that by the third day without sleep even substantial rewards were unsuccessful in maintaining performance. This study is important because it demonstrates both the powerful effect of sleep deprivation and the substantial ability individuals have for combating fatigue, at least for moderate durations.

Most sleep deprivation researchers know that individuals differ in their ability to withstand fatigue. Some subjects show remarkable resiliency, demonstrating little variance in their mood and performance, while others fluctuate widely. But since researchers often are more interested in elucidating the general principles of sleep deprivation, individual differences get averaged out in the drive to find main effects and interactions. Hill, Welch and Godfrey [54] on the other hand, have directly investigated the contribution of certain personality traits, specifically locus of control, on mood during 26-30 hrs of sleep deprivation. "Those who believe that ability, effort and hard work will lead to positive outcomes are said to have an internal locus of control. Those who believe that events are determined by fate or other uncontrollable factors are said to have an external locus of control." (Hill, p.41 [54]). From a pool of 61 subjects these authors chose 28 individuals half of whom scored high (external group) on a questionnaire for locus of control and half of whom scored low (internal locus of control group). They found that mood disturbances after sleep loss were quite apparent for individuals with external locus of control, but individuals with internal locus of control showed few if any mood disturbances.

Table 1

TASK VARIABLES	AMPLIFIES SD EFFECTS	REDUCES SD EFFECTS
Duration	Long	Short
Difficulty	Hard	Easy
Pacing	Work-paced	Self-paced
Complexity	Low	High
Proficiency	Novice	Expert
Feedback	No	Yes
Memory Load	Great	None

The preceding two examples (i.e., of motivation and individual differences) illustrate the importance of psychological variables as modifiers of mood and performance during sleep loss. Johnson's second sub-class of non-task variables is situational factors, which include exercise, noise, ambient temperature, drugs and breaks (among others). With the exception of the new stimulant 'modafinil' to be discussed in part two of this paper, other reports in this volume will review the effects of drugs on performance. Angus, Heslegrave and Myles [1] and more recently Horne and Foster [59] and LeDuc, Caldwell and Ruyak [76] have investigated the effects of exercise on mood and performance. The general conclusion is that exercise does have alerting effects on mood and performance but that these effects are short lived. Furthermore, "people who use exercise as an intervention for maintaining alertness during periods of sleep loss may end up more sleepy than if they had not exercised" (LeDuc, p.265 [76]).

It is interesting to speculate whether the alerting effect of exercise is due less to physical exertion and more due to the arousal value of engaging in any activity that breaks up the monotony often associated with sleep loss studies. Pigeau and Angus [96] illustrated the positive (but short-lived) effect that a 15-minute break every 1 hr and 45 min can have on performance. The oscillation in performance for the serial reaction task observed in Plot A of Figure 6 is due to the ameliorative effect of the break. Plot C shows the effect more clearly. Complex demodulation was used to subtract the linear and circadian components (Plot B) from the raw data, leaving only the residual (Plot C). Each of the elevated points in Plot C occurred after the break and the lower points occurred 1 hr into the work session. If the original serial

reaction time data are plotted separately (see Figure 9, Plot A), the influence of the break is more apparent. More importantly, after a break the fatigue effect on performance (i.e., the linear decline) is less pronounced than when the task is given 1 hr later (After Break slope= -1.14; 1 hr into Session slope= -1.34). Contrast this effect with that for the logical reasoning task (Plot C, Figure 7). There the oscillation is almost non-existent and appears more random. When the data are plotted separately for the two conditions (see Plot A, Figure 10) the slopes are identical with very little space between the regression lines. The logical reasoning task, therefore, perhaps because it is a more complex task, is more resilient to break effects though still showing considerable overall effects due to sleep loss (recall Figure 7, Plot A).

The final non-task variable that Johnson describes is behavioural periodicity (the rhythmical variable). The most common and pervasive periodicity observed in sleep deprivation studies – if the data are collected frequently enough to measure it – is the circadian component (1 cycle/day). We have already discussed the technique of complex demodulation (CD) and its usefulness for extracting rhythmicities in sleep deprivation results. CD was used to extract the circadian component of Stanford Sleepiness data (Figure 5), for the serial reaction task (Figure 6, Plot B) and for the logical reasoning task (Figure 7, Plot B). Using CD it is also possible to demonstrate that the break effect mentioned earlier for the serial reaction task manifests itself differently in the circadian component – that is, the effect appears not only in the linear component. Plot B in Figure 9 clearly shows a difference in the circadian amplitude between the two conditions for the first 24 hrs of sleep deprivation. The circadian effect for after-break performance is 'dampened' initially and then increases in amplitude as sleep deprivation progresses. For performance occurring 1 hr into the session, the amplitude of the circadian component is larger, and remains large throughout the sleep loss period. For the logical reasoning task (Plot B, Figure 10), however, the circadian component for both conditions are almost identical – again showing that this task is more resistant to breaks effects (though nonetheless sensitive to sleep deprivation overall).

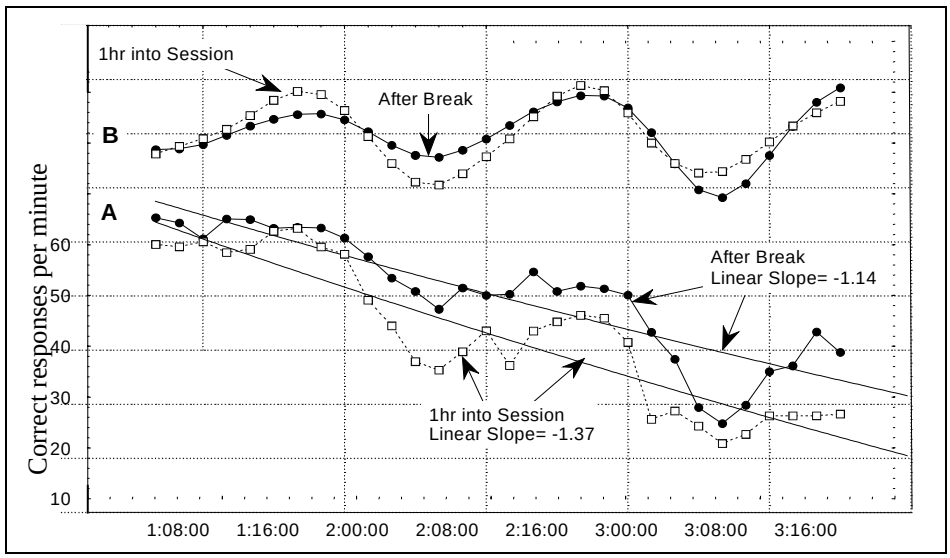

Figure 9: Serial Reaction Time

The circadian influence on performance is present in most sleep deprivation studies that sample at least twice a day. Other rhythms have also been identified (e.g., 2 cycles/day, see Babkoff [3]). Indeed, the dominance of rhythmicities in sleep deprivation studies has prompted Babkoff et al. [3] to suggest that they should have a more prominent position in Johnson's taxonomy than simply being relegated to a sub-class status of non-task variables. They suggest that behavioural periodicities should have first level status – equivalent to fatigue, task and non-task variables. We agree with this conclusion and suggest further that all rhythmicities should really be classified as a particular type of the fatigue (or amount-of-prior-wakefulness) variable (see top circle in Figure 11). We have argued previously that fatigue and sleepiness are confounded; that it is almost impossible to separate one effect from the other. And although it is possible to extract a linear component from sleep deprivation data (and thus call it a fatigue effect), it is probably more appropriate to describe this effect as curvilinear rather than linear. After all, sooner or later performance must asymptote due to floor and ceiling effects in the data – i.e., performance can degrade only to the limit of the lowest possible score of the task being performed. Therefore, fatigue may be more appropriately classified as a second-degree polynomial rather than a first-degree polynomial. The

circadian component (sleepiness?) could then be classified as a third-degree polynomial. A 2 cycle per day rhythm (i.e., an ultradian rhythm) could be classified as a fifth-degree polynomial – and so on.

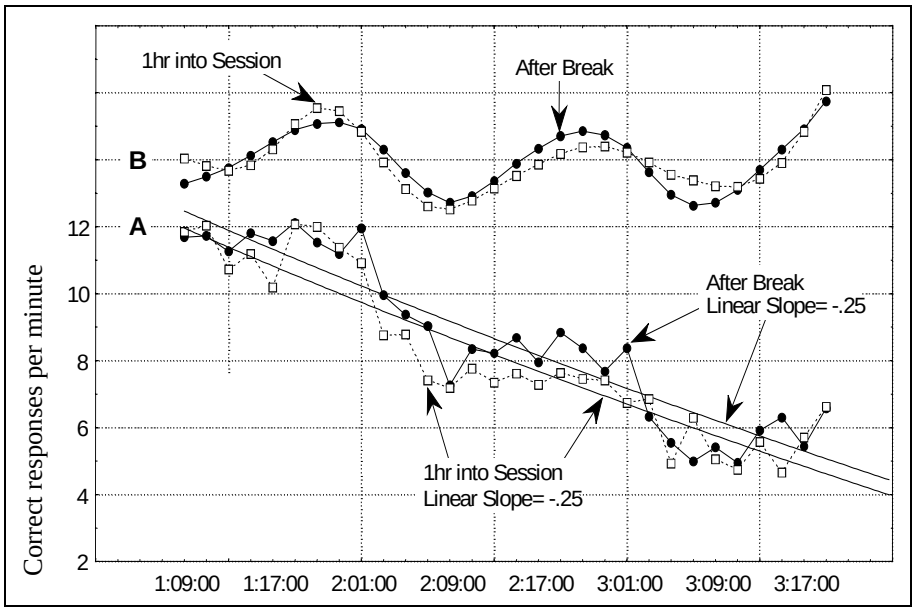

Figure 10: Logical Reasoning Task

Regardless of which taxonomy one uses to describe effects due to sleep deprivation, it is clear that all of these variables can interact among themselves and with each other (see Figure 11). Multiple task variables (e.g., difficulty and duration) can operate at once and influence non-task variables (e.g., motivation and breaks), which in turn effect and can be affected by fatigue and sleepiness. With all of these possible intereactions it should not be surprising that sleep deprivation has proven to be a complex field of study.

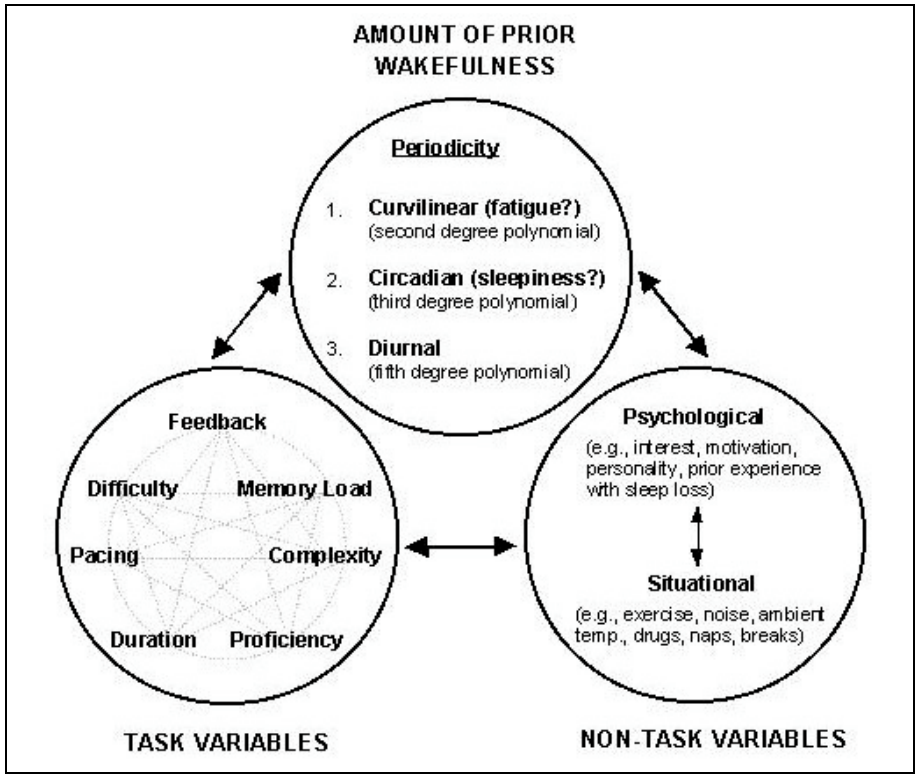

Figure 11: Effects due to sleep deprivation

Before concluding this overview of sleep deprivation, it is worth considering two possible explanations for the effects of sleep loss. The first is the lapse hypothesis originally mentioned by Bjerner [16] and then extended upon by Williams et al. [109]. The second is a hypothesis concerning the role of the pre-frontal cortex in sleep loss [50, 51]. The lapse hypothesis suggests that declines in performance during sleep

deprivation are due to ‘lapses’ in arousal. These lapses may last from 1 to 10 seconds and manifest themselves as ‘microsleeps’ where subjects are unresponsive to stimuli. To researchers who have studied total sleep deprivation, lapses in performance are common among subjects, with these lapses sometimes lasting as long as 20 seconds or more, requiring experimenters to intervene and wake the subject up. The lapse hypothesis predicts that performance effects due to sleep loss result predominantly in longer reaction times rather than fewer numbers of correct responses. For example, Angus and Heslegrave [1] found that the number of responses per minute for serial reaction, logical reasoning and encoding/decoding tasks all decreased with increasing sleep deprivation, but that the number of errors remained unchanged. Koslowsky and Babkoff [66] in their meta-analysis of 27 sleep deprivation studies lasting longer than 45 hrs found that correlations were highest for measures of speed rather than accuracy and for work-paced tasks rather than self-paced tasks. They viewed these results as consistent with the lapse hypothesis.

The lapse hypothesis suggests that if subjects are not suffering from microsleeps then their performance should be close to baselines levels, which in turn suggests that performance deficits are due mainly to the propensity to fall asleep rather than to any ‘slowing’ of cognitive activity. However, there is a growing body of literature [37, 48-50, 58, 105] that suggests sleep deprivation affects the pre-frontal cortex, an area of the brain that is associated with temporal memory, innovation, divergent thinking and word fluency.

> The PFC [pre-frontal cortex] directs, sustains and focuses attention to the task in hand by disregarding competing distraction and is the executive coordinator of many cortical events. Inasmuch as with practice and training most complex tasks lose their novelty and become more routine, then in these respects, they become less dependent on the PFC. (Harrison, p.246 [50])

In their review of the impact of sleep deprivation on decision-making, Harrison and Horne [51] argue that the cognitive tasks used in most sleep loss studies are boring, over learned and novelty-free (like serial reaction, logical reasoning, subtraction, addition, etc.). Such tasks are susceptible to lapses in arousal (i.e., susceptible to microsleeps) during extended periods of wakefulness and thus should demonstrate longer response latencies or fewer responses per unit time. Novel tasks, on the other hand, require higher cognitive functions (e.g., naturalistic decision-making, see Klein, [64]) that may be more real world oriented and require flexibility and adaptability. As we have seen from Johnson’s taxonomy, these tasks may be more resistant to de-arousal (i.e., sleepiness) but Harrison and Horne maintain that they nonetheless demonstrate reductions in accuracy and effectiveness due to ‘fatigue’ of the pre-frontal cortex.

> Despite the paucity of studies concerning executive-type decision making following SD [sleep deprivation], we have highlighted several areas for concern: impaired language skills – communication, lack of innovation, inflexibility of thought processes, inappropriate attention to peripheral concerns or distraction, over-reliance on previous strategies, unwillingness to try out novel strategies, unreliable memory for when events occurred, change in mood including loss of empathy with colleagues, and inability to deal with surprise and the unexpected. (Harrison, p.246 [50])

It is our belief that the tension between fatigue and sleepiness – i.e., are they different, are they the same? – that we raised in the section on ‘Measures of Sleepiness and Fatigue’, now finds expression in the two hypotheses for explaining performance deficits during sleep deprivation. The lapse hypothesis assumes that all declines in performance are due to sleepiness (i.e., propensity to fall asleep), whereas a more global notion of fatigue is implicated for tasks involving the pre-frontal cortex. As we will see, these two viewpoints will also influence how one interprets the results from studies investigating the effect of the new stimulant modafinil.

Part Two: Ameliorative Effects of Modafinil

Consistent with Johnson’s [62] taxonomy, among the possible non-task (situational) variables that can modify the effects of sleep deprivation are naps, drugs, breaks, physical fitness and exercise. We have briefly discussed the positive but short-term effects on performance that both exercise and breaks can have on sleep loss. And although few studies have looked at physical fitness, Angus, Pigeau and Heslegrave [2] do mention that when they compared iron triathletes with normally fit individuals, no differences were found in their ability to withstand the cognitive effects of sleep deprivation.

There is no question that the most potent remedy for sleep loss is sleep; the question becomes how much sleep? Obviously the answer should be the longer the better. But if extended sleep is not possible, short naps have been found to moderate the effect of sleep loss (see Caldwell, this volume). But if naps are not possible (say for operational reasons), sometimes the only alternative to sleep is pharmaceutical intervention. Lagarde [73] has divided alerting substances (or psychostimulants) into three classes: amphetaminic substances, xanthine derivatives, and new synthetics. The first (e.g., d-amphetamine) have potent pharmacological and psychological effects including feelings of euphoria, loss of appetite, increases in heart rate and blood pressure, while the second (e.g., caffeine) have fewer side effects but also reduced potency [75, 88]. Amphetamine and caffeine are discussed in detail by Caldwell and Lagarde (this volume). The third class of psychostimulants, called eugregoric (*eu* meaning *good*, and *gregor* meaning *wakefulness* [75]), have recently become available and purport to have alerting properties similar to amphetaminic substances. For the remainder of the present paper we will review evidence for the ameliorative effects of a new eugregoric psychostimulant called modafinil.

Modafinil

Modafinil [(diphenyl-methyl) sulphinyl-2-acetamide] is described as a substance that maintains wakefulness while having few side-effects [69]. It appears to produce no feelings of euphoria, does not seem to be addicting, induces no drug tolerance and in extremely large dosages (>4500 mg) does not cause death [80]. Among its minor side-effects are "headache, nausea, slight tachycardia, salivation, anorexia, sweating, cutaneous eruptions, unrest or aggressiveness, and occasional insomnia" (Buguet, p.230 [23]) – these symptoms having been reported in narcolepsy patients (e.g., see [8, 14, 17]). Nevertheless, the relatively benign psychopharmacological properties of modafinil make it a good candidate for reducing or ameliorating the effects of total sleep deprivation, particularly in military operations [60] Indeed, modafinil was used to positive effect in operation Desert Storm during the Gulf War by the French military [74].

The pharmacological mechanism of modafinil is not well known. It has been described as an alpha-1 adrenergic agonist [80, 98] but more recent studies [41] have shown that modafinil inhibits γ-aminobutyric acid (GABA) release in the cerebral cortex through the possible involvement of serotonergic receptors leading to secondary increases in dopamine levels [42, 43, 83]. However, "unlike amphetamine, a well-known dopaminergic transmission-enhancing drug, and other psychostimulants, modafinil induces long-lasting…[wakefulness] without causing marked behavioural excitation and subsequent sleep rebound" [78 p.90]. Slow wave sleep (SWS) rebound during recovery sleep is a well-known event in sleep-deprived subjects. Amphetamine disrupts this process by increasing the number of awakenings during recovery sleep. In fact, the poorer sleep efficiency observed among subjects who have taken amphetamine often necessitates a second recovery sleep period before sleep topology returns to normal [23]. Caldwell and Caldwell [26] also found that amphetamine elicited recovery sleep that was "less restful than the sleep following placebo, but more restful than baseline, predeprivation sleep" (p.99). Modafinil on the other hand allows recovery sleep to occur which is similar to that experienced by a placebo group [23].

Lin et al., [78] hypothesize that amphetamine acts as a general central nervous system (CNS) stimulant affecting a large number of cortical neurons, whereas modafinil's effects are more focused, perhaps limited to the anterior hypothalamus or to the forebrain ascending disinhibitory pathways. The result is that amphetamine maintains wakefulness by stimulating the CNS while modafinil "increases waking by inhibiting sleep mechanisms originating from the anterior hypothalamus" (Jouvet, p.7-1 [60]).

> In the presence of such disinhibition, the cerebral cortex would be maintained in an activated state by natural influxes originating from various ascending systems… and neither these ascending systems nor brain waking executive structures, such as the thalamus and cerebral cortex, would be excessively activated or excited (Lin, p.95 [75])

This hypothesized difference in mechanism between amphetamine and modafinil is consistent with reports of their effect on experience. Pigeau et al., [92] reported that 2 hrs after drug ingestion subjects given 20 mg of amphetamine felt 'great' and experienced a 'kick', while subjects given 300 mg of modafinil simply stated that they did not feel tired. If modafinil maintains wakefulness by inhibiting sleepiness rather than

by exciting the CNS, this may account for the 'overconfidence' effect seen with modafinil after 48 hrs of sleep loss [5]. However, before discussing this possibility, we will first briefly review modafinil's effects on performance.

Until recently, there has been a paucity of research investigating the ameliorative effects of modafinil on performance using normal adult subjects. Modafinil has been used primarily in either clinical studies to treat sleeping disorders [8, 12, 13, 15, 69-71] or in animal studies to investigate its pharmacological properties [38, 52, 73, 84, 103]. Of the earlier studies performed on healthy human adults, none has investigated the relative effectiveness of modafinil under sleep loss conditions involving more than 1 night or under continuous workload conditions [11, 75, 102]. The results of Bensimon *et al*. [11], where healthy subjects displayed positive effects of modafinil after a single night of sleep loss with low workload, are encouraging but cannot be extended to include more extreme workload conditions. Lagarde and Batejat's [75] study, where 200 mg of modafinil was administered to eight subjects three times a day in a 60 hrs sleep loss experiment is more conclusive. Performance on a variety of cognitive tasks was maintained by modafinil, compared to placebo controls, for approximately 44 hours, thereafter performance declined to placebo levels.

In one of our own drug studies [92] subjects were given either 20 mg of d-amphetamine, 300 mg of modafinil or a placebo at three different times during 64 hrs of total sleep deprivation. The first treatment occurred at 23:30 of the first night without sleep to determine if the stimulants would counteract the expected decline in performance. The second was given 30 hours later at 05:30 after the second night without sleep to investigate whether the stimulants would recuperate performance. And the third dose was given at 15:30 after 57 hours of wakefulness to investigate modafinil and amphetamine's effect on recovery sleep. Figures 12 and 13 display the results from two items of a questionnaire given every two hours. Subjects were asked on a scale from 0 to 5 whether they agreed (a rating of 5) or disagreed (a rating of 0) with the statements 'I feel good' and 'I feel alert'. The figures clearly show the effects of amphetamine and modafinil vs. placebo after both the first and the second drug treatments. The placebo group rated themselves as feeling less 'good' and less 'alert' from midnight of the first night without sleep until approximately 10:00 the next day. While the subjective estimates for the amphetamine and the modafinil groups were quite high during this period and they do deteriorate by 04:00 of the second morning – the drugs being metabolized by that time – reaching the same levels as the placebo group. Estimates jump again for the amphetamine and modafinil groups with administration of the second drug treatment at 05:30[4].

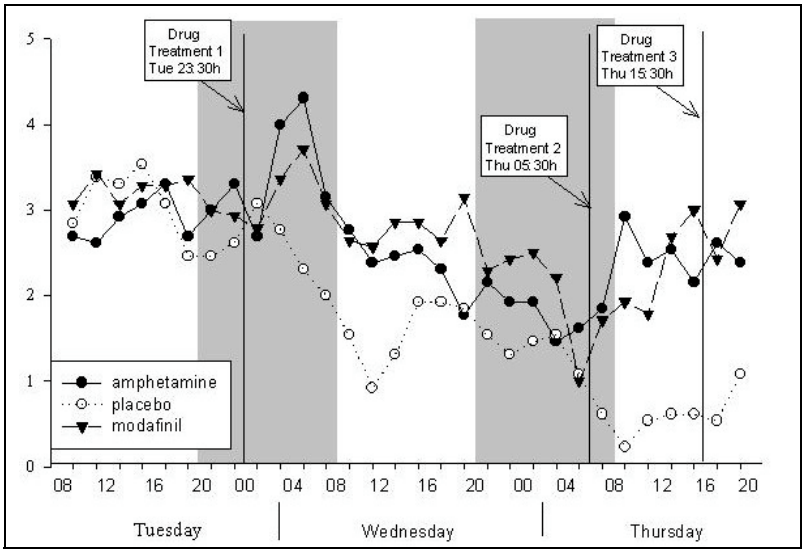

Figure 12: I Feel Alert

The effects on performance were very similar. Figures 14 and 15 show the results for the serial reaction and the logical reasoning tasks. In this case, each subject's data were complex demodulated with the linear

[4] When the subjects were allowed recovery sleep that evening, the third drug treatment had the expected effect on sleep latency. Subjects in the placebo group took on average 9 minutes to fall asleep whereas the amphetamine and modafinil groups took 24 and 26 minutes respectfully.

and circadian components extracted yielding a new 'clean' data set that was then averaged for each drug group (see Pigeau and Naitoh [95]) The effects of modafinil and amphetamine are clearly evident.

At the end of the experiment, before the subjects left the laboratory, a 1 hr structured debrief was conducted where a standard list of questions was asked. One question asked subjects to list the symptoms that they experienced during the study (the subjects were not informed of drug condition they were in until three months later). Of the total number of symptoms listed 45% (189 out of 418) were experienced by the amphetamine group, 35% (147/418) by the modafinil group and 20% (82/418) by the placebo group. The only notable symptom reported by the modafinil group was increased frequency of urination and a slightly higher propensity to have headaches.

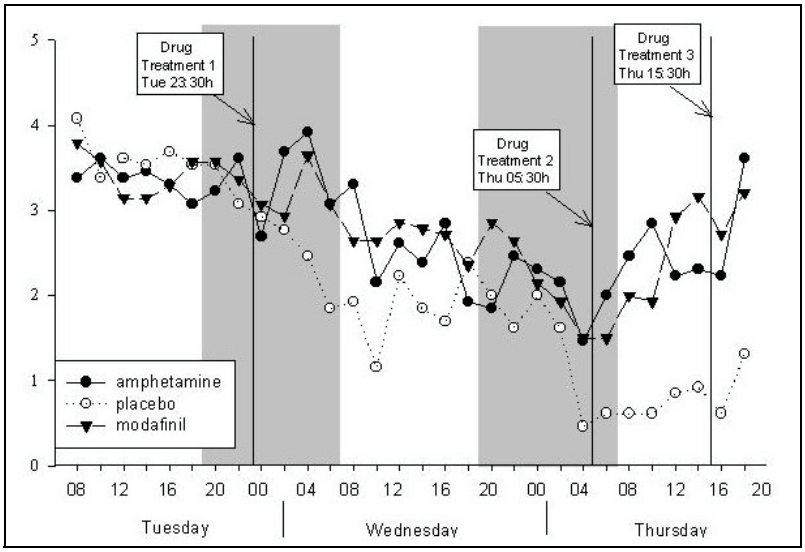

Figure 13: I Feel Good

In another 64 hr sleep deprivation experiment, Baranski et al., [6] demonstrated a dose-related response to modafinil. In this study a preventative paradigm was used where modafinil was given every eight hours throughout the sleep deprivation period (starting at 20:00 of the first night). Four dose conditions were tested: 300 mg within a 24 hr period (100 mg/8 hr); 150 mg within a 24 hr period (50 mg/8 hr); 50 mg within a 24 hr period (16.7 mg/8 hr); and placebo. They found that a dose of 100 mg/8 hr maintained performance near baseline levels throughout the sleep deprivation period. The 50 mg/8 hr dosage was only moderately successful and, interestingly, the 16.7 mg/8 hr dosage yielded differences only for certain tasks.

> Although 300 mg of modafinil (100 mg/8 hr) clearly outperformed the alternative drug conditions on each of the measures that showed a sleep-deprivation effect, a systematic dose-response curve was not clearly evident for each measure. For example, for several measures (e.g., alertness, serial reaction time), 50 mg of modafinil closely paralleled 150 mg of modafinil, whereas for other measures (e.g., motivation, short-term memory), 50 mg of modafinil was virtually indistinguishable from the placebo. (Baranski, p.189 [6])

At low dosages, therefore, the ameliorative effects of modafinil seem to be dependent on some of the modifier variables reviewed in Part 1.

The efficacy of modafinil to moderate performance declines due to sleep loss has also been compared with the beneficial effects of naps. Pigeau and Angus [96] used the data reported by Pigeau et al. [92] and compared them to results from previous studies where 2 hr naps were given at times coincident with two of the three drug treatments. Specifically, 2 hr naps were given at 22:00-24:00 of the first night without sleep and in another study at 04:00-06:00 after the second night without sleep. Recall that in the amphetamine and modafinil study, the first drug treatment was given at 23:30 of the first night (so that by 24:00 the drugs would take effect) and at 05:30 the second morning. The results showed that both modafinil and amphetamine were more effective than a 2 hr nap to resist performance degradation during the first night without sleep, but that they were only as effective as a 2 hr nap after 48 hrs of wakefulness. Modafinil, amphetamine and a 2 hr nap recuperated performance to the previous day's level (i.e., after 24 hrs of sleep deprivation), but they were not sufficient to return performance to baseline levels. Whether giving modafinil in addition to a 2 hr nap would be sufficient to recover baseline performance is an interesting

question. The findings of Batejat and Lagarde [9] suggests that the effects of modafinil and a nap could, in fact, be additive.

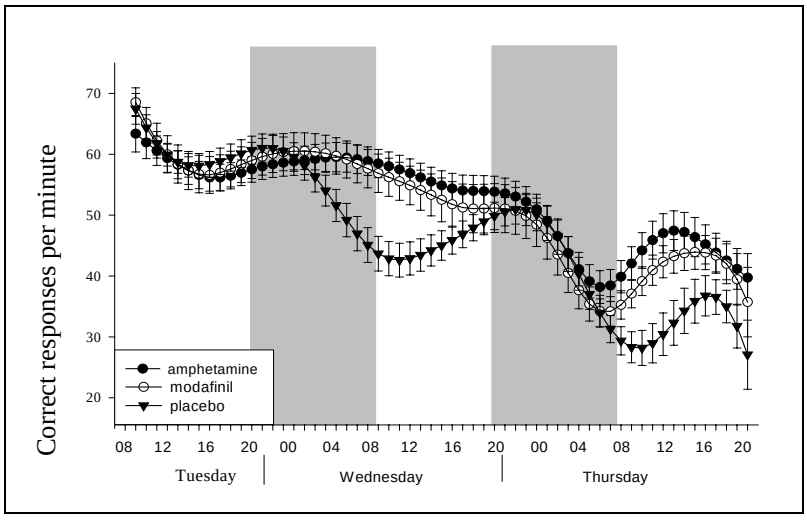

Figure 14: Linear and circadian trend data for the Serial Reaction Task

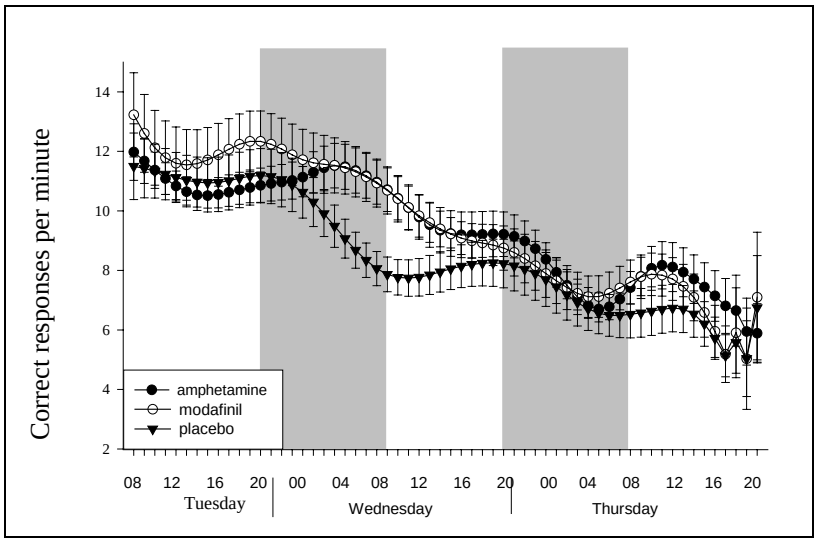

Figure 15: Linear and circadian trend data for the Logical Reasoning Task

Caldwell et al. [25] using a more real-world task also found that 200 mg doses of modafinil attenuated sleep loss effects compared to placebos for 4 of 6 helicopter flight manoeuvres. Yet as encouraging as the effects are for modafinil, they do not come without potential risks. At high dosages (e.g., 600-800 mg/day), modafinil elicits a dose-dependent effect on anxiety, insomnia and blood pressure [72]. Caldwell et al., [25] found that helicopter pilots flying simulator flights experienced vertigo, nausea and dizziness. Modafinil has also been shown to affect thermoregulation [21, 22, 92] by increasing core body temperature. Baranski et al., [7] recently replicated this finding but found no adverse effects on psychological performance (nor on physiology [81]).

The most intriguing finding concerning modafinil, however, is the 'overconfidence' effect reported by Baranski and Pigeau [5]. In the modafinil-amphetamine study already described (Pigeau et al [92]), two of the many tasks that subjects were required to perform were a perceptual comparison task and a mental addition task. Immediately prior to each task, subjects were asked to estimate the percentage of trials that they thought they *would* answer correctly. Also, immediately after each task, the subjects were asked to estimate the percentage of trials that they thought they *had* answered correctly. By comparing each subject's assessments with his or her actual performance, estimates of over-confidence (i.e., performing more poorly than estimated), under-confidence (i.e., performing better than estimated) or good calibration (i.e., estimates matching performance) could be calculated. From an earlier sleep deprivation study, Baranski et al. [4] found that subjects were remarkably good at assessing their performance – that is, they were *well calibrated* throughout the sleep deprivation period. Despite the fact that performance degraded

as a function of sleep loss, subjects were able to correctly assess their degraded performance (no feedback was provided). In other words, there was no sleep loss effect on the ability to self-monitor performance. This finding was replicated in the placebo group of the drug study by Baranski and Pigeau [5]. Interestingly, the amphetamine group also showed good calibration. The modafinil group, however, displayed a consistent tendency for overconfidence approximately 2 hrs after drug ingestion. At a dosage of 300 mg, modafinil apparently impaired the ability to self-monitor; but more importantly, it impaired self-monitoring ability in a potentially dangerous direction. If declines in performance due to sleep loss are over-estimated (i.e., leading to under-confidence in one's own abilities), individuals may adopt cautious strategies for dealing with fatigue. On the other hand, if declines in performance are under-estimated (leading to over-confidence as found with the modafinil group), individuals may adopt strategies that could compromise their safety – e.g., not pulling their car over to the side of the road when they are very tired.

We had briefly stated in Part 1 that answering subjective questionnaires was a meta-cognitive act requiring the seemingly effortless but psychologically fascinating ability to self-monitor. We also showed that subjects were poor in distinguishing the difference between fatigue and sleepiness by showing that subjective estimates of fatigue and sleepiness were highly correlated. Finally, we discussed that there may indeed be a difference between fatigue and sleepiness insofar that fatigue resulted from declining pre-frontal cortex abilities and sleepiness from circadian pressures for sleep onset. We hypothesize that the key to explaining the over-confidence effect with modafinil may lie in the relationship among meta-cognition, the pre-frontal cortex and sleepiness. The remainder of this paper will explore this possibility.

Meta-cognition, sleepiness and fatigue.

Meta-cognition is defined as "individuals' knowledge of the states and processes of their own mind and/or their ability to control or modify these states and processes" (Gavelek and Raphael, [45], p. 105 as cited in Cohen and Freeman, [30], p.209). According to this definition, subjectively attempting to assess one's fatigue and sleepiness is meta-cognition, as would attempting to assess one's performance in a task. The difference between them is that assessing sleepiness is a relatively direct interrogation of an internal state (i.e., propensity for sleep or 'How much would I like to fall asleep right now?') whereas assessing performance requires both an assessment of sleepiness and an assessment of temporal memory (i.e., 'How well or poorly did I perform last time?'). In Baranski and Pigeau's [5] self-monitoring task subjects were asked to predict their performance before doing the task (pre-task estimates) and to estimate their performance after doing the task (post-task estimates). Both required recalling past events: in the case of pre-task estimates it required recalling how the subject felt they had performed on the previous invocation of the task; and for post-task estimates it required recalling and assessing their performance for the past 10 or more minutes. Harrison and Horne [50] have shown that temporal memory is affected by sleep deprivation. In a task given only once after 35 hrs of sleep deprivation, subjects were exposed to photographs of human faces presented at a rate of 1 picture every 10 sec. Two sets of 12 photographs were presented in this manner with the sets themselves (set A and set B) presented 5 minutes apart. These photographs were considered the target set. Five minutes later a stimulus set of 48 photographs (containing the original 24 targets plus 24 photographs not previously seen) were presented with the subjects' task both to identify whether they had seen the faces before (recognition) and whether the faces had come from set A or set B (temporal memory). The results showed that recognition of faces was not impaired with sleep loss when compared to a control group who had not been sleep deprived. Temporal memory, however, was affected. Sleep deprived subjects were poorer in their ability to determine whether they had seen the faces in set A or set B. Furthermore, when the subjects were asked to give a confidence estimate on the temporal memory portion of the task sleep deprived subjects were more confident in the accuracy of their *wrong* responses than the control group. There was no difference between the groups in their confidence on the accuracy of correct responses. Harrison and Horne argued that temporal memory is linked to the pre-frontal cortex citing evidence from medical studies showing similar deficits among patient with pre-frontal cortex lesions.

Recall that the most recent hypothesis for the mechanism of modafinil is that it inhibits sleep mechanisms originating in the anterior hypothalamus. Modafinil inhibits the natural tendency for sleepiness that comes with sustained wakefulness. It is not a general CNS stimulant as amphetamine is. Therefore, although subjects report not feeling sleepy after taking modafinil and can perform well-learned tasks more easily – that is, tasks that minimally involve the pre-frontal cortex – they may nonetheless be suffering from pre-frontal cortex fatigue. To the extent that confidence estimates involve temporal memory, and temporal memory requires pre-frontal cortex abilities, the overconfidence effect observed for modafinil may be due to pre-frontal cortex fatigue. The amphetamine group on the other hand showed good calibration because both sleepiness and pre-frontal cortex fatigue is reduced due to overall increases in CNS arousal.

The last piece of the puzzle is to explain why the placebo group does not also demonstrate an over-confidence effect; after all, their pre-frontal cortex must be as fatigued as that of the modafinil group. We hypothesize that the answer lies in the close correlation between feelings of sleepiness and poor performance. Placebo subjects report high levels of subjective fatigue and sleepiness (recall Figure 1) with extended sleep loss. We believe that subjects can use this subjective experience of sleepiness as a cue for predicting level of performance. With the sleepiness cue removed, however, as it is when modafinil is taken, subjects have recourse only to temporal memory for making their confidence assessments – a temporal memory that may be compromised due to pre-frontal cortex fatigue. It is important to stress that both sleepiness cues and temporal memory are hypothesized as being necessary for making confidence assessments. This would suggest that even placebo subjects should, eventually, show an overconfidence effect as pre-frontal fatigue increases. Harrison and Horne's [50] overconfidence result for temporal memory after 35 hrs of sleep loss is consistent with this interpretation. Also, careful perusal of Figure 1 from Baranski and Pigeau's [5] report shows that the placebo group does demonstrate over-confidence after 48 hrs of sleep loss.

This possible explanation for the over-confidence effect with modafinil has two empirically testable implications. First, tasks involving the pre-frontal cortex should not be ameliorated by modafinil during sleep deprivation. Subjects may feel alert but their ability to perform novel, higher-level cognitive tasks should still be compromised. Therefore tasks requiring speech [48], divergent thinking [49] and temporal memory [50] – i.e., tasks involving the pre-frontal cortex – should be as susceptible to sleep loss with modafinil as with a placebo. Second, performance on these tasks should not be affected when a general CNS stimulant like amphetamine is taken.

As appealing as this possibility may be for explaining the overconfidence effect, there are two results in the literature that potentially weaken the argument. First, Baranski, Pigeau and Angus [4] showed that confidence is remarkably well calibrated throughout 48 hrs of sleep loss. They found neither over-confidence nor under confidence while subjects performed a mental addition task, despite significant declines in response times and accuracy due to sleep loss. It should be noted, however, that these authors collected confidence ratings on each set of numbers being added. That is, during a 15 min session subjects performed approximately 50 separate iterations of mental additions. Hence, confidence ratings were being collected every 15 to 20 seconds, a situation that hardly taxes the subject's temporal memory. Contrast this to the pre- and post-task estimates gathered 10 min apart in Baranski and Pigeau's [5] report.

The second and more problematic finding is from Baranski et al. [7]. Using the same pre- and post-task paradigm for gathering confidence assessments, no over-confidence effects were found for subjects deprived of sleep for 40 hrs and given modafinil. Although the general conditions for this study were markedly different from those described in the earlier Baranski and Pigeau [5] study – e.g., the exercise regime, the thermal conditions, the intermittent testing – the only difference of note for our purpose was dosage. Baranski et al. [7] gave 300 mg per 24 hrs (100 mg/8 hrs) whereas Baranski and Pigeau gave single dosages of 300 mg. Considering that higher doses of modafinil have produced side effects (e.g., blood pressure [69] and nausea [25]), perhaps the overconfidence effect similarly does not appear until higher doses are used.

It is important to stress, however, that regardless of the validity of the overconfidence effect, modafinil seems to be a safe and worthy alternative to amphetamine for counteracting the debilitating effects of sleep deprivation particularly when well learned and thoroughly practiced tasks are involved.

Conclusion

The allure of sleep deprivation as a topic of scientific inquiry is matched only by its attraction to the general public. The popular media is replete with segments discussing sleep or sleep deprivation, with even academics writing popular books for the lay reader (e.g., Coran, [31]; Dement, [34]). Whether the attraction is due to the existence of a chronic shortage of sleep in our fast paced Western society (as Coran, [31] argues) or whether it is due to the safety issues that can arise from sleep loss, research in sleep and sleep deprivation is thriving. The primary purpose of this paper was to introduce to the reader the major issues associated with total sleep deprivation and then to discuss one of the ways effects due to sleep loss can be ameliorated (i.e., with modafinil).

Total sleep deprivation was emphasized because it establishes 'the worst case scenario' for fatigue; it bounds the extremes of the problem space allowing standards for comparing the effects of partial sleep

deprivation and sleep disruption – e.g., due to shift work, jet lag, operational necessity, illness, etc. As we have seen, there is more to sleep deprivation than simply getting tired. The word 'tired' itself can be interpreted either as the propensity for falling asleep (i.e., sleepiness) or it can mean a general condition of cortical fatigue (i.e., specifically the pre-frontal cortex). In the first case, the outcome is dangerous because it can negatively affect tasks requiring vigilance and quick response (like driving a car or monitoring safety systems). In the second case, high-level cognitive and meta-cognitive tasks may be compromised. Although there are many other possible benefits to sleep (e.g., memory consolidation, growth, dreaming, etc) the recuperative role it serves for cognitive functions must rank among the highest.

When sleep is not possible, however, the best short-term solution may be stimulants. Amphetamine has been used for many years, but the drug is known to have side effects that can be dangerous. The new eugregoric drug modafinil has potential for being a safer alternative. The most recent research suggests that it produces it effects by inhibiting naturally occurring sleep mechanisms. It seems not to act as a general central nervous system arouser, like amphetamine. It should, therefore, perhaps not be classified as a stimulant at all. If this interpretation is correct, then modafinil ameliorates only one aspect of sleep deprivation – i.e., sleepiness – and will be effective only for maintaining well-learned and well-practiced cognitive tasks. Its ability to counteract fatigue, with its purported effects on higher-level cognitive tasks, remains in doubt. Regardless, finding suitable countermeasures for sleep loss seems to be a priority for our society, particularly if we insist on sacrificing our natural mechanism for recovering cognitive performance: that is, sleep.

Acknowledgement

I would like to thank Andrea Hawton for her invaluable assistance during the preparation of this manuscript.

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Jet-Lag Syndrome

Barbara M. Stone
QINETIQ Centre for Human Sciences
Cody Technology Park
Building A50, Ively Road
Farnborough, Hampshire GU14 0LX
United Kingdom

ABSTRACT

Rapid travel across time zones leads to a lack of synchrony between the activity of the internal rhythm generating systems of an individual and the local social or environmental time cues of the new time zone. The internal circadian clock adapts slowly to this mismatch leading to the syndrome known as jet-lag. This syndrome is particularly characterised by sleep disturbances, reduced daytime alertness and performance, gastrointestinal symptoms and a general feeling of malaise. These symptoms are obviously undesirable for service personnel who are involved in intensive and sustained operations and who may have to deploy to a location involving travel across several time zones. Following north–south travel there are no problems with jet lag (Buck et al., 1989)

The adaptation of the circadian clock may take around one hour per day without countermeasures to adapt to a new time zone. However, around one third of travellers do not experience jet lag. In particular sleep disturbance is experienced by around 78% of subjects after a transmeridian flight whereas after 3 nights only around 30% of subjects experienced disturbance. In another study 40% of subjects reported subjective weakness.

There have been a number of studies on the effects of transmeridian flight on sleep. In general the severity of the sleep disturbance following transmeridian flight is related to the direction of travel and to the number of time zones crossed. Following eastward flight and when sleep is scheduled in advance of the home time zone there may be difficulties falling asleep and problems awakening in the morning. These difficulties may not be seen on the first night in the new time zone as if the flight involves an overnight flight without sleep. Such sleep problems may persist for several days and reductions in SWS and REM sleep may be present. After westward flights the sleep disturbance may only last for two or three days. Sleep quality is good in the first part of the night, with increased SWS on the first night associated with the long period without sleep. On subsequent nights an increase in REM sleep has been observed.

Recently reports of temporal lobe atrophy, spatial cognitive deficits in cabin crew chronically exposed to repetitive transmeridian flight have appeared in the literature. However, military personnel are unlikely to be subjected to frequent time zone changes.

Time zone travel in military operations

In scenarios involving sustained and continuous operations personnel may be required to be effective very soon after a rapid time zone transition. Moreover, soldiers, sailors and airmen may not have the time available for adaptation that is considered to be necessary for the efficient performance of business travellers or airline pilots.

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

For example, during the Gulf War, many military units underwent a rapid transmeridian deployment and were then required to begin 24h operations as soon as they arrived (Ferrer et al., 1995) They were therefore faced with the problem of working throughout the 24 hour period against a background of jet-lag.

Circadian mechanisms.

Circadian rhythms are believed to be internally generated from the central pacemaker, the suprachiasmatic nucleus (SCN), in the hypothalamus. Most circadian rhythms also have an exogenous component due to a direct interaction with the environment. For example sleep lowers body temperature and exercise raises body temperature. Therefore the rhythm which we observe measure or experience is the sum of the endogenous and exogenous influences. The exogenous influences are referred to as *masking*. The problems of jet lag are considered to be due to the endogenous component of the rhythm.

The natural circadian rhythms of man are synchronised to the environmental and social cues of the environment. This synchronisation is maintained by cues, 'timegivers' or zeigebers.. The intrinsic tau or phase of the circadian pacemaker is considered to be around 24.2-24,3h. Daily phase adjustments are made to counteract the tendency of this pacemaker to delay and to keep human rhythms entrained to the 24h day. After transmeridian travel the synchronisers in the environment are no longer in synchrony with the circadian rhythm of the individual. It is the inability of the rhythms of the individual to adapt rapidly to a sudden shift of these external synchronisers that causes a short-term dysynchronisation or mismatch between the body and the environment. Light is considered to be the stronger synchroniser of circadian rhythms to the 24 hour day (Wildgruber et al., 1983, Czeisler, 1995)

Symptoms

After transmeridian flight this mismatch leads to a series of symptoms which in some individuals lead to a subjective loss of well-being and to objective disturbance in sleep and performance. This syndrome, known as jet-lag, is characterised by sleep disturbances, reduced daytime alertness and performance, gastrointestinal symptoms, loss of appetite, distortion of time and distance, loss of physical strength and a requirement to urinate during the night. and a general feeling of malaise. The organisation of the menstrual cycle in females may also be disturbed (Voge, 1996). Meals eaten out of phase with the internal clock may give rise to inappropriate pancreatic and metabolic responses, some of which may be long term risk factors for heart disease (Hampton et al., 1996). These symptoms are obviously undesirable for service personnel who are involved in intensive and sustained operations. Even if subjective symptoms are not present the rhythms of an individual may require several days to adapt to the new time zone. The jet lag phenomena was first described in detail by Strughold (1952) and comprehensively reviewed by Klein and Wegmann (1979).

The internal circadian clock adapts slowly to abrupt changes of time cues. The rate of adaptation has been reported to follow a number of models. Rates of one hour per day without countermeasures, or quicker adaptation during the first days have all been quoted. However, since the adaptation is highly dependent on the individual, to the direction of flight, to the number of time zones crossed, to exposure to environmental cues any simplistic formula is inappropriate. The direction of the time zone change is particularly important. In general adaptation after eastbound travel is much slower than after westbound flight. Gander et al. (1989) showed that it took several days for the acrophase of the temperature rhythm to come within one standard error of complete resynchronization after a 9h westward transition, and that the adaptation in an eastward direction took even longer. This differing rate of adaptation related to direction of travel is shown in table 1 (after Klein and Wegmann, 1979). This table also shows the differing rates of

adaptation of various physiological and psychological variables. The average rates of adaptation do not take into account the swifter adaptation immediately after travel.

VARIABLE	WESTBOUND	EASTBOUND
Body temperature	60	39
Reaction time	150	74
Heart rate	90	60
Urinary 17-OHCS	47	32

Table 1. Shift rates after transmeridian flight in minutes per day

In addition to differing speed of adaptation depending on direction of travel, it is also relatively common for travellers to adapt in the 'wrong' direction, such as delaying 16h instead of advancing 8h. (Gundel and Wegmann, 1989)

Around one third of travellers do not experience jet lag. But for those who do it is particularly associated with disturbance in sleep patterns.

Sleep patterns

In studies in the United Kingdom the sleep and circadian rhythms of following both westward and eastward flight have been studied in volunteer subjects and in aircrew. In a joint study with the Henry Ford Hospital in Detroit the adaptation to a 5h shift in both directions was studied (Nicholson et al., 1986).

Healthy male volunteers were studied for two days before, for 8 days in Detroit, and after the return flight to London on an overnight flight they were studied for a further 5 nights and 4 days. Sleep was recorded by electroencephalography and sleepiness during the day was assessed by the multiple sleep latency test. The study also included a condition where a hypnotic was used to counteract the jet lag but another speaker will cover this topic and I will only consider the results with placebo. Sleep with placebo after westward and eastward flights were compared with sleep during the control period. On the first night after the westward flight subjects fell asleep more quickly, but there was more awake activity and drowsy sleep during the second part of the night. (Fig 1).

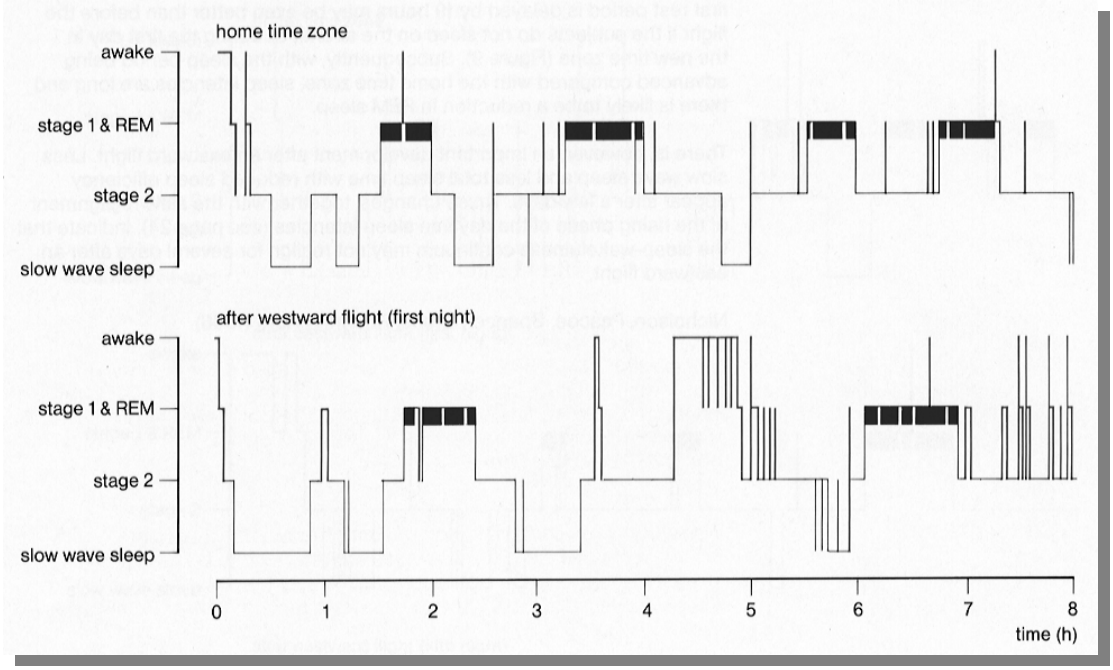

Figure 1

Sleep after five-hour westward flight. On the first night sleep onset was rapid but the second half of the night was disturbed.

The fast sleep onset reflects the requirement to sleep at a time equivalent to a late bedtime in the home time zone. The disturbed sleep in the second part of the night relates to the requirement to stay asleep around the equivalent of lunchtime in the home time zone. The late bedtime leads to a slight sleep deprivation that increases slow wave sleep and reduces the amount of Rapid Eye movement (REM) sleep. (Taub and Berger, 1973, Webb and Agnew 1971) During the second and third nights after westward flight s the ratio of REM to non-REM sleep was raised. This is due to the natural circadian rhythm in REM sleep that peaks towards the end of the normal sleep period. (Nicholson et al., 1984). This change in ratio was not seen on the first night because slow-wave sleep was increased. By the fourth night a normal sleep pattern was established, and together with the realignment of the rising phase of daytime alertness, which was seen at the same time, indicated that sleep had adapted to the new time zone.

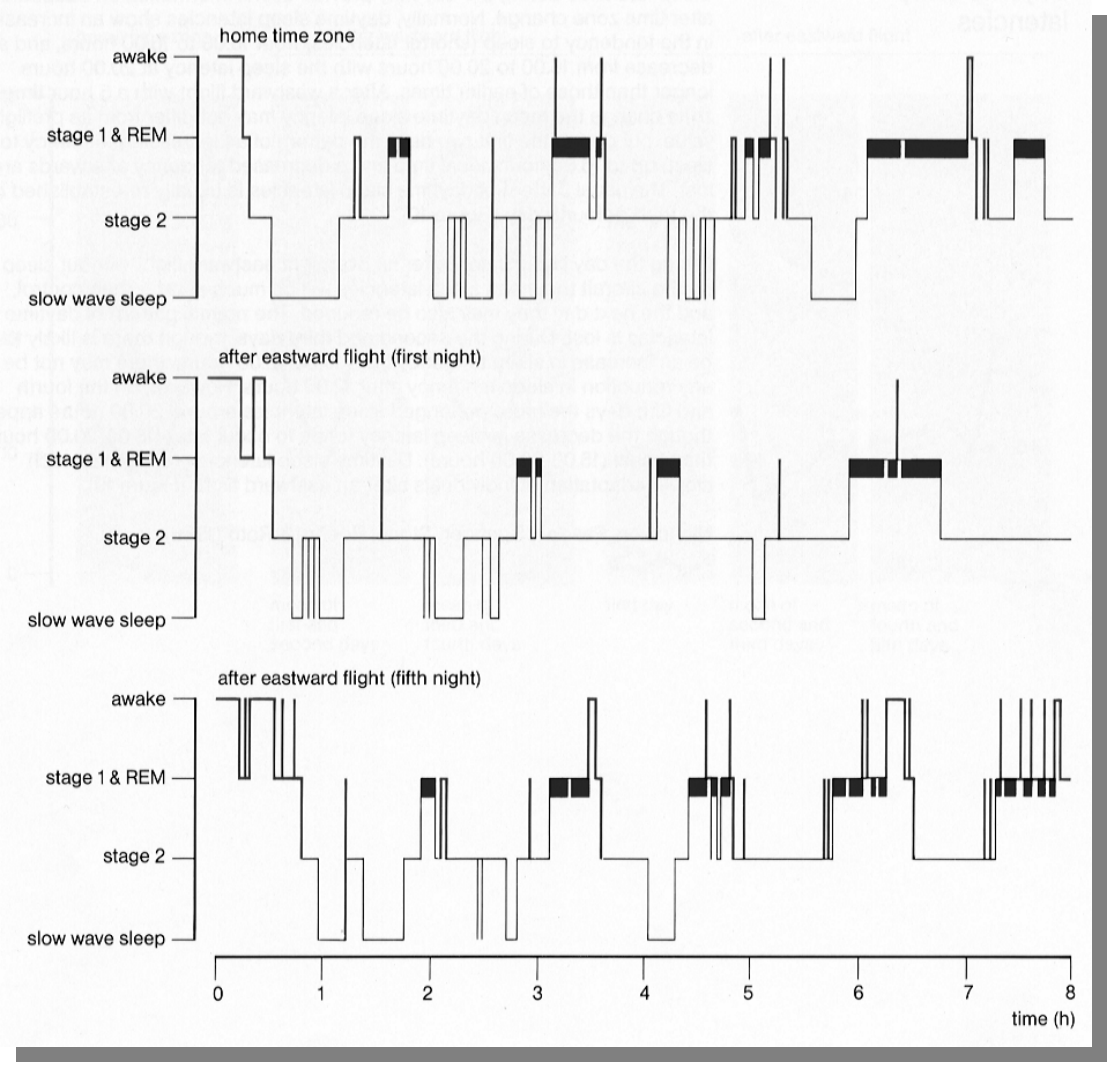

Figure 2

Sleep after five-hour eastward flight. On the first night sleep after an overnight flight sleep was not disturbed. On subsequent nights sleep onset was delayed and this was still apparent on the fifth night.

After eastward fight (Fig 2) the subjects slept better than before the flight. The eastward flight was overnight and this caused a delay of 19h in the first rest period, therefore on this first night the subjects were sleep deprived and slept quite well. The ratio of REM to non-REM sleep was also reduced. On the second night the subjects took longer to fall asleep reflecting the requirement to fall asleep at equivalent to 1830 in the time zone to which they were adapted. This difficulty in falling asleep persisted for the rest of the study. As well as difficulties in falling asleep, subjects also had reduced slow-wave sleep on the fourth night. On the fifth night which was the final recording night, total sleep time and sleep efficiency were reduced. The relatively slow adaptation after eastward flight may be related to the natural period of the circadian rhythm that is slightly longer than 24 hours. This study of a relatively small time zone change confirmed that adaptation to eastward travel is slower than adaptation to westward travel. By the end of five days back in the home time zone sleep and daytime alertness were not fully adapted after eastward flight and this slower adaptation is proportionately worse after a greater time-zone difference.

Gundel and Wegmann (1987) also demonstrated the longer adaptation after a 9h eastward transition, as well as large differences in the pattern of adaptation, with 3 out of 12 individuals experiencing a phase delay rather than a phase advance. Aircrew flying the polar route between London and Tokyo (Spencer et < biblio >) exhibited similar complex patterns of adaptation, with large individual differences.

In an attempt to predict the pattern of adaptation of aircrew and other travellers to rapid time-zone transitions, Gundel and Spencer (1992) developed a model based on the van der Pol equation. This equation has formed the basis for models of the human circadian system (Kronauer, 1984), and has been used to represent the effects of light on the circadian pacemaker (Kronauer, 1990). The model of Gundel and Spencer is based on the forced van der Pol equation:
The same authors have recently (1999) fitted the output from the model to body temperature data recorded before and immediately after a 10h eastward transition between London and Sydney. This 10h eastward time-zone change was chosen because simulations suggested that the pattern of adaptation would be most sensitive to changes in the parameter values making up the model. The fitting procedure also allowed for masking effects.

Twelve subjects were divided into two groups of 6, and each group completed an eastward flight between London, departing at 1300h local time, and Sydney, arriving at 1945h local time on the following day. Throughout the study, each subject kept a record of his daily activities in a logbook. This included the timing of sleep, meals, drinks, showers and exercise. Sydney is approximately 150º east of London, corresponding to a 10h difference. Recordings were made during a baseline period before departure, for a continuous 8-day period on arrival in Sydney and, after two days off, for a further two-day period before the return flight to London.
At 1min intervals throughout the study, rectal temperature was recorded on a Squirrel digital logger (Grant Instruments (Cambridge) Ltd). To reduce the effect of masking by activity and environmental changes, four 45min-rest periods were scheduled at approximately equal intervals during the day.
Only the temperature recordings during sleep and the rest periods were used for the estimation of circadian rhythmicity.
The adaptation of the 12 subjects to the 10-hour eastward transition is illustrated in Figure 3. This figure displays the estimates of acrophase on consecutive days after the flight, based on the estimated values of the individual sets of parameter values. Eleven subjects adapted by delaying his circadian clock, while only one adapted by advancing it. Those who delayed had adapted to within one hour of the new time zone after 8 days, whereas the one who advanced was adapted to within one hour after 6 days. During the time when the circadian acrophases were changing rapidly, the amplitudes of the rhythms were reduced to between 2% and 52% of the entrained values.

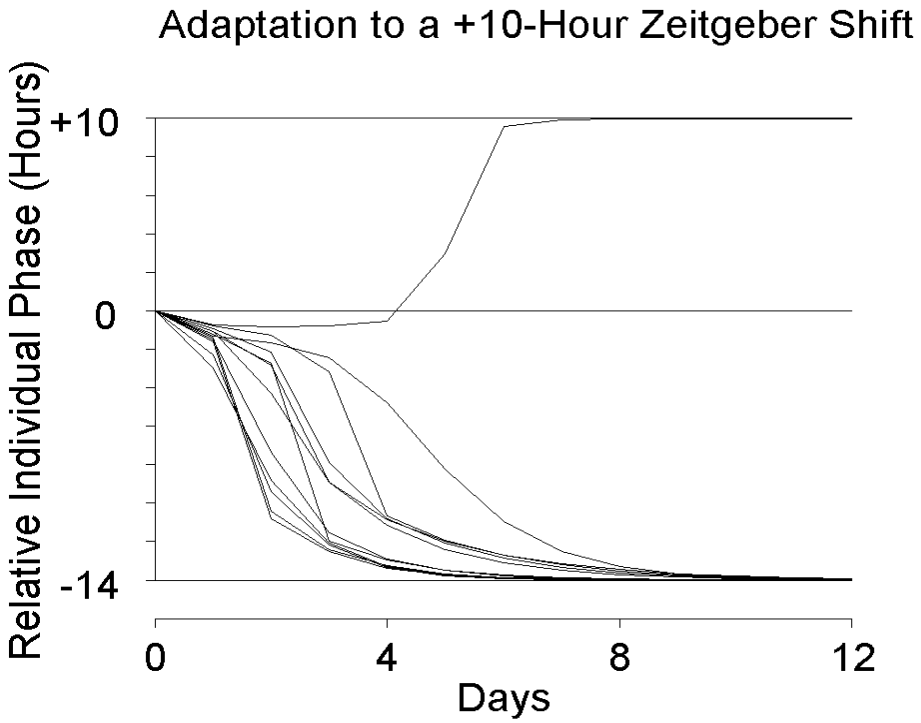

Figure 3

Circadian phases estimated from simulations using the estimated model parameters. Most of the twelve subjects respond to the 10-hour shift by a delay of the circadian time, the other one by an advance. Day 1 is the first day in the new time zone

The consequences of individual differences were also examined. Adaptation times were in a range between 1 and 11 days. However, weaker zeitgebers will generally lead to much longer adaptation times, and it has already been stressed that the zeitgebers in this study are likely to have been stronger than those that would normally be experienced, for example by aircrew on layover or military personnel on deployment. Since the prediction of adaptation times is dependent on the choice of the external force, estimates may need to be more conservative in real life situations when light exposure cannot be measured. This study emphasised the enormous individual differences in adaptation of the circadian. to long eastward time zone transitions. Performance rhythms also adaptation to a new time zone is also direction sensitive. Like physiological measures performance adapts more slowly after eastward flight and greater decrements in performance are observed after eastward travel. (Klein et al., 1970) The rate of adaptation also appears to be influenced by the complexity of the task. The more complex tasks are more sensitive to time zone crossings. This has obvious military implications.

The light-dark cycle is the principal time cue for resetting human circadian rhythms. If light of a suitable intensity and duration is administered both phase delay and phase advance of rhythms can be achieved. There are few field studies on the use or influence of light to speed adaptation to jet lag. In a military scenario light boxes may not be readily available! However, the judicious avoidance of light at particular times may be useful. For example, when travelling east over more than four or five time zones and arriving in the early morning, subjects will experience light, which opposes their adaptation. The use of blinds on the plane and eye masks on arrival may avoid this opposing light.

Long term health effects

It has been generally accepted that the main problem of the jet lag syndrome is the associated sleep disturbance. This sleep disturbance exacerbates the lowered performance associated with operating at the circadian low. Research has been focused on improving sleep by pharmacological and other means. Countermeasures to jet lag will be considered elsewhere. Apart from the sleep disturbance and the associated fatigue it was generally believed that jet lag is a mild inconvenience. However, in a recent study (Cho, (2001) has suggested that long term repeated time zone changes impair physiological and psychological health and induce stress. Cortisol levels in cabin crew after repeated exposure to transmeridian travel were higher than those exposed to short distance flights. (Cho et al., 2000) these higher cortisol levels were associated with cognitive deficits. It has been suggested that high cortisol levels lead to hippocampal atrophy and reduction in hippocampus dependent learning and memory. (Porter and Landfield, 1998, Lupien et al., 1998) In the study by Cho (2001) the log-term effect of repeated jet lag on the volume of the temporal lobe and hippocampus-dependent memory performance were tested in air stewardesses.

The temporal lobe was measured by MRI scan. The right temporal lobe was reported to be smaller in the group who had less than a five-day interval between outward transmeridian flights. These differences were reported to be unrelated to short-term sleep deprivation. The authors suggested that a longer recovery period may have eliminated the damage.

Military subjects are unlikely to be exposed to frequent time zone changes and therefore these findings are not yet a cause for concern in service personnel. However, if the changes are related to continuous circadian rhythm disturbance, this may have implications for military personnel who regularly work around the clock.

CONCLUSION

The performance of military personnel is likely to be compromised by transmeridian flight when they are required to deploy on arrival. One third of the personnel may suffer no ill effects. Eastward travel will cause more problems than westward travel and countermeasures should be considered and where necessary implemented.

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Efficacy of Napping Strategies to Counter the Effects of Sleep Deprivation

J. Lynn Caldwell, Ph.D.
U.S. Army Aeromedical Research Laboratory
P.O. Box 620577
Fort Rucker, AL 36362-0577, USA

E-mail: Lynn.Caldwell@SE.AMEDD.army.mil

INTRODUCTION

There is an abundance of evidence indicating that a nap taken during long periods of otherwise continuous wakefulness is extremely beneficial for improving alertness and performance (Bonnet, 1990; 1991; Dinges, Whitehouse, Orne, and Orne, 1988; Lorizio, Terzano, Parrino, Cesana, and Priore, 1990; Matsumoto and Harada, 1994; Rogers, Spencer, Stone, and Nicholson, 1989; Rosa, 1993; Webb, 1987). However, scheduling naps is not a simple matter. Several factors are important to consider before implementing a napping regime into a continuous operations scenario.

Nap timing

One important factor in scheduling naps is placing them at optimal times with regard to the amount of sleep loss. A nap taken during the day before an all-night work shift (a prophylactic nap), with no sleep loss prior to the shift, will result in improved performance over the night compared to performance without the nap. Although naps taken later in the sleep-deprivation period also are beneficial, these naps probably should be longer than prophylactic naps in order to derive the same performance benefit. Schweitzer, Muehlback, and Walsh (1992) measured performance and alertness in subjects who received a 2- to 3-hour nap before a night work shift (with concurrent sleep loss). Although the usual circadian trough was seen in the early morning, the nap attenuated the decline in performance compared to a night where no nap was taken prior to the shift.

In a study conducted by Bonnet (1991), a nap before a 52-hour continuous performance period was beneficial in keeping performance and alertness from decreasing for up to 24 hours compared to the no-nap condition. However, by the second night of sleep loss, the benefit of the naps could not be reliably measured. In a study by Naitoh and colleagues (Naitoh, Englund, and Ryman, 1982), subjects were given a 3-hour nap after being awake for approximately 24 hours, but then were required to stay awake an additional 20 hours. Results indicated that this 3-hour nap reduced the decline in performance during the additional work period. Naps taken prior to extended periods of sleep loss, "prophylactic naps," do not totally eliminate the circadian dip seen in the early morning (around 0500); however, the degradation in both cognitive performance and alertness is attenuated compared to no napping conditions (Bonnet, 1990; Carskadon and Dement, 1982; Gillberg, 1984; Haslam, 1985; Nicholson et al., 1985).

Nap length

Another factor to consider when scheduling naps during continuous operations is nap length. Most studies indicate that naps from 1 hour to 8 hours will improve performance and alertness during continuous operations. A relationship between nap length and performance was reported by Bonnet (1991) based on a study in which subjects were allowed either a 2, 4, or 8-hour nap before 52 hours of continuous operations. The results indicated a dose-response relationship between the length of the nap and performance during the first 24 hours of sleep deprivation. Bonnet concluded that the nap before an all-night shift should be as long as possible to produce maximum performance benefits, and that prophylactic naps were better than naps designed to replace sleep that was already lost due to requirements for continuous wakefulness.

An investigation by Lumley and colleagues (Lumley, Roehrs, Zorick, Lamphere, and Roth, 1986) in which subjects were deprived of sleep for 24 hours and then permitted naps of either 15, 30, 60, or 120 minutes, indicated that alertness increased as a function of increased nap length, with the highest level of alertness occurring after the 60-minute nap. There was, however, no difference between the 60-minute nap and the 120-minute nap, possibly due to sleep fragmentation in the longer period.

Nap placement and the circadian phase

Another factor to consider when planning a napping strategy for use during continuous operations

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

is where the nap should be placed in the circadian phase. Nap timing should take into account the ease of falling asleep at various times, the quality of sleep as a function of the body's internal clock, and the effects on performance both immediately after awakening and later in the work period. Sleep tendency is highest when core body temperature is in its trough (in the early morning hours) and lowest when core body temperature is in its peak (in the early evening hours) (Dinges, 1986). Thus, there may be significant problems initiating and/or maintaining a nap during times when core temperature is high, termed the forbidden zone for sleep (Lavie, 1986).

Naps which are placed during the circadian troughs are the easiest to maintain, and they show beneficial effects on later performance. When naps placed in the circadian trough are compared to naps placed in the circadian peak, the effects on performance are different. Gillberg (1984) examined the effects of a 1-hour nap placed either at 2100 or 0430 after 24 hours of sleep deprivation. Both naps improved performance the following morning when compared to a no-nap group, but the nap taken at 0430 (in the circadian trough) showed the most benefit. While a nap taken anywhere in the circadian cycle before sleep deprivation is beneficial in maintaining performance across the sleep loss period, there is a high cost to napping during the early morning (during the circadian trough). Although naps during the circadian trough may be more effective for performance sustainment (and they are easier to initiate and maintain), they also are the more difficult naps from which to awaken. Generally, studies have shown that post-nap sleepiness, termed “sleep inertia,” is higher and performance is lower immediately upon awakening from a nap taken during the circadian trough as compared to naps taken during the circadian peak (Dinges, Orne, and Orne, 1985).

Regardless of the time of the nap, sleep inertia will occur, and work requirements should be delayed accordingly. Performance generally will be lowest during the first 5 minutes after awakening, but it usually recovers after 15 to 30 minutes (Dinges et al., 1985). Generally, sleep inertia will be extended in situations where the timing of the nap is misplaced and/or the amount of sleep deprivation is extensive before the nap occurs. Thus, Dinges et al. (1985) suggest that during continuous operations, naps in the circadian trough should be avoided, and naps should be taken before a person's sleep loss extends beyond 36 hours. However, it should be possible to take advantage of the improved quality of naps in the circadian trough while avoiding the sleep-inertia effects if napping personnel can be awakened about 1 hour prior to their work shifts.

SUMMARY

In summary, naps are beneficial for reducing sleepiness and performance decrements during sleep-deprivation periods. However, before scheduling naps during continuous operations, several factors should be taken into account. A nap is most beneficial if taken before significant sleep loss occurs, if it is as long as possible, and if it is placed in the circadian trough (provided there is time to recover from sleep inertia).

Unfortunately, work demands and staff shortages make scheduling naps in the real world problematic. It may not be possible to schedule naps during times when personnel will find it easy to sleep (during circadian troughs). In addition, the anxiety, noise, heat, and environmental lighting present in operational scenarios may impair the ability of personnel to initiate and maintain effective sleep. Thus, in order to provide a way for personnel to obtain needed sleep whenever the opportunity to sleep occurs, a short-acting sleeping aid such as zolpidem tartrate may be useful.

Zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class, is supplied in 5 and 10 mg tablets for oral administration (Physician Desk Reference, 1998). It has a mean elimination half-life of 1.7 hours (se=0.1) (Thenot et al., 1988) and few daytime residual effects (Blois, Gaillard, Attali, and Coquelin, 1993). The recommended dose is 10 mg given immediately before bedtime. Most studies indicate that next-day performance is not affected by nighttime administration of 5 or 10 mg of zolpidem tartrate (Quera-Salva et al., 1994; Richens, Mercer, Jones, Griffiths, and Marshall, 1993; Sanger et al., 1987; Sicard, Troucherie, Moreau, Vielillefond, and Court, 1993). Higher dosages (20 mg) have been found to mildly affect next-day performance (Balkan, O’Donnell, Wesensten, McCann, and Balance, 1992), but even at this dosage, there have been few residual effects (Bensimon et al., 1990).

STUDY QUESTIONS

Since research indicates that taking a nap prior to sleep loss can help offset performance decrements seen during extended work schedules, napping should be beneficial in sustained operations. However, if people are unable to place naps at optimal times or if they are unable to sleep because of situational factors (i.e., heat, noise, light), zolpidem tartrate may be useful.

The first question addressed by this experiment was whether a 2-hour nap, placed late in the evening (during the “forbidden sleep zone”), would affect the performance, mood, and sleepiness of aviators during a continuous operations scenario. The

second question was whether zolpidem tartrate could be effectively used to promote naps (and thus enhance the performance-sustaining effects of naps) during times when sleep was not expected to come readily.

METHOD

Subjects

Eighteen male aviators between the ages of 22 and 31 (mean of 24.4) and weighing between 145 and 205 pounds (mean of 177.6) participated after medical pre-screening.

Procedure

During three sleep deprivation periods, subjects completed cognitive tests, electrophysiological evaluations, and questionnaires. Subjects were tested following a 2-hour nap induced with zolpidem (Znap), a 2-hour nap without zolpidem (Pnap), and a 2-hour forced-rest period (Nonap). The study was fully counterbalanced and double-blind.

Testing schedule. Subjects were tested in pairs and were housed in the U.S. Army Aeromedical Research Laboratory (USAARL) throughout the 9-day testing period. Subjects reported to USAARL on Sunday for electrode attachment, initial training on the cognitive task, and an adaptation sleep night. On Monday, training began at 0900 after 10 hours of sleep and lasted until 2010 (bedtime was at 2200). On Tuesday, Thursday, and Saturday (the control/intervention days), testing was conducted at the same times as on Monday following 10-hours of sleep; however, rather than receiving a full night's sleep on each of these nights, subjects received one of the interventions--either Pnap, Znap, or Nonap, beginning at 2100 and ending at 2300. All subjects received all three interventions, with subjects being randomly assigned to one of the six possible orders of interventions with the constraint that the orders be fully counterbalanced. On Wednesday, Friday, and Sunday (the test days following interventions), subjects began testing at 0100 and continued until 2010. On the last Monday (following the last sleep-deprivation period), testing was conducted throughout the day. On Tuesday, subjects were released after 10 hours of recovery sleep. Control days (Tuesday, Thursday, and Saturday) were placed between each test day to allow complete drug clearance and recovery from sleep deprivation prior to the next intervention. Subjects were supervised at all times. The schedule is shown in figure 1.

Visual Analog Scale (VAS). The VAS was administered hourly from 0900 to 2000 on control days (and again at 2300 after the nap or forced rest) and from 0100 to 2000 on test days. Subjects rated themselves by marking 100 mm lines centered over the adjectives: “alert/able to concentrate,” “anxious,” “energetic,” “feel confident,” “irritable,” “jittery/nervous,” “sleepy,” and “talkative” (Penetar et al., 1993) At the ends of each line, “not at all” and “extremely” were printed, respectively. Scores for each adjective consisted of the distance (in millimeters) from the left edge of the line to the mark.

Repeated test of sustained wakefulness (RTSW). The RTSW was performed every 2 hours, beginning at 1010 and ending at 2010 on control days, and from 0210 to 2010 on test days. The subject, who attempted to remain awake while reclined on a bed with eyes closed in a cool, darkened bedroom, was allowed to remain in bed for as long as 20 minutes, but was immediately awakened if he fell asleep. Electroencephalographic (EEG) data were recorded from C3, C4, O1, and O2 referenced to contralateral mastoids (A1 or A2) and scored to determine the time from lights out until the first occurrence of a K complex or sleep spindle. A Nihon Koden electroencephalograph (EEG-4321P) was used with time constants and high filter settings of 0.3 sec. and 35 Hz, respectively.

Sleep architecture of naps. Polysomnograms during naps also were collected with a Nihon Kohden. EEG, electrooculogram (EOG) and electromyogram (EMG) data were recorded throughout the napping periods to assess sleep quality. EEG data were recorded from C3, C4, O1, and O2 referenced to contralateral mastoids; EOG data were recorded from electrodes placed at the outer canthus of the left and right eyes; and EMG data were recorded from electrodes attached submentally. Time constants and high filter settings were the same as the RTSW for the EEG; they were set at 5.0 sec. and 10.0 Hz for the EOG, and 0.003 sec. and 120 Hz for the EMG. Nap records were scored according to standard procedures (Rechtschaffen and Kales, 1968) in terms of sleep latency (lights out until the first full minute of stage 2), percentage of time spent in each stage, movement time, and time awake after sleep onset.

Profile of Mood States (POMS). The POMS was administered every 2 hours, beginning at 0900 and ending at 1900 on control days, and from 0100 to 1900 on test days. The POMS is a 65-adjective scale yielding 6 scores: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment (McNair, Lorr, and Droppleman, 1981). Subjects were asked to indicate how well each of the mood adjectives described their present feelings. Scores for each of the 6 factors were calculated using template-guided scoring.

Multi-attribute task battery (MATB). The MATB was completed every 4 hours, beginning at 0910 and ending at 1710 on control days, and from 0110 to 1710 on test days. The MATB, a 30-minute, computerized, aviation simulation test, required monitoring simulated aircraft fuel levels (resource management) and warning lights/dials (systems monitoring), while concurrently completing an

Time	Sunday	Monday Training	Tuesday Baseline	Wednesday Test	Thursday Recovery	Friday Test	Saturday Recovery	Sunday Test	Monday Recovery	Tuesday
0100				VAS/POMS		VAS/POMS		VAS/POMS		
0110				MATB		MATB		MATB		
0200				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0235				EEG/EP		EEG/EP		EEG/EP		
0300				VAS/POMS		VAS/POMS		VAS/POMS		
0330				MiniSim		MiniSim		MiniSim		
0400				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0500				VAS/POMS		VAS/POMS		VAS/POMS		
0510				MATB		MATB		MATB		
0600				VAS/RTSW		VAS/RTSW		VAS/RTSW		
0635				EEG/EP		EEG/EP		EEG/EP		
0700				VAS/POMS		VAS/POMS		VAS/POMS		
0730				MiniSim		MiniSim		MiniSim		
0800		Wakeup	Wakeup	VAS/RTSW	Wakeup	VAS/RTSW	Wakeup	VAS/RTSW	Wakeup	Wakeup
0830		Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast	Breakfast
0900 0910		VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	Debrief
1000		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	Release
1035		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1100		VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1130		MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	
1200		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1235		Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	Lunch	
1300		VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1310		MATB	MATB	MATB	MATB	MATB	MATB	MATB	MATB	
1400		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1435		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1500	Arrive	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1530	Inservice	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	
1600	Medical	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1700 1710	Electrode Hook-up	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	VAS/POMS MATB	
1800	Hook-up	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
1835		EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	EEG/EP	
1900	Dinner	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	VAS/POMS	
1930	Training	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	MiniSim	
2000		VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	VAS/RTSW	
2035		Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	Dinner	
2100		PT	Drug/nap	PT	Drug/nap	PT	Drug/Nap	PT	PT	
2130	Vitals	PT/Shower	OR Rest	PT/Shower	OR Rest	PT/Shower	OR Rest	PT/Shower	PT/Shower	
2205	**Lights out**	**Lights out**		**Lights out**		**Lights out**		**Lights out**	**Lights out**	
2300			Wakeup/VAS		Wakeup/VAS		Wakeup/VAS			
2400			Shower		Shower		Shower			

Figure 1. Testing schedule.
VAS - Visual Analogue Scale; POMS - Profile of Mood States; MATB - Multi-attribute Task Battery; RTSW - Repeated Test of Sustained Wakefulness; EEG - Resting electroencephalogram; EP - evoked potentials; PT - Physical training (exercise)

Nighttime sleep

Nap/rest period

unstable tracking task and a communications task (following auditory instructions to change "radio frequencies"). Subjects were scored in terms of how quickly and accurately they responded. Specifically, the resource management task yielded mean deviation of units of fuel in tanks A and B from the target of 2500; systems monitoring yielded mean reaction time (RT), standard deviation of RT (SDRT), and time-out errors for lights and dials; communications yielded number of time-out errors and mean RT and SDRT for correct responses; and tracking yielded root mean square (RMS) deviations.

Medication administration. Each zolpidem tartrate tablet (10 mg), placed in a white capsule, which matched lactose-filled placebos, was administered at 2230 (30 minutes prior to nap time) with approximately 8 ounces of cold water.

RESULTS

Analysis of variance (ANOVA) with repeated measures on two factors (condition and time) was used to analyze the data (except for the sleep data in which there was only a condition factor). To maintain brevity, only effects which involve the condition factor will be discussed.

Sleep architecture of naps

Nap data were analyzed with a one-way ANOVA for condition (Znap and Pnap). The variables were minutes in bed; minutes until sleep onset; minutes of sleep; percentage of stages 1, 2, 3, 4, and rapid eye movement (REM); percentage of time awake after sleep onset; and movement time. Because one subject was unable to sleep during his zolpidem nap (on the second night of the study) despite being able to sleep during his placebo nap (on the fourth night), his data were excluded from the analysis. The results indicated that there was faster sleep onset, greater minutes of sleep, less stage 1 sleep, and more stage 4 sleep after zolpidem than placebo (see figure 2).

RTSW

The RTSWs, analyzed in a 2-way ANOVA for condition (Znap, Pnap, and Nonap) and time (0210, 0410, 0610, 0810, 1010, 1210, 1410, 1610, 1810, and 2010), indicated a condition-by-time interaction and a condition main effect. The interaction was because differences among the conditions were larger during the first half than the second half of the day (see figure 3). Subjects were better able to remain awake after Znap than after Nonap throughout the testing day; Pnap was better than Nonap except at 1410 and 1610; and Znap was better than Pnap at 0410, 0610, 1210, 1610, and 2010. The condition main effect showed Znap led to improved wakefulness compared to the other interventions, and Pnap was better than Nonap (means were 11.7, 9.4, and 6.3, respectively).

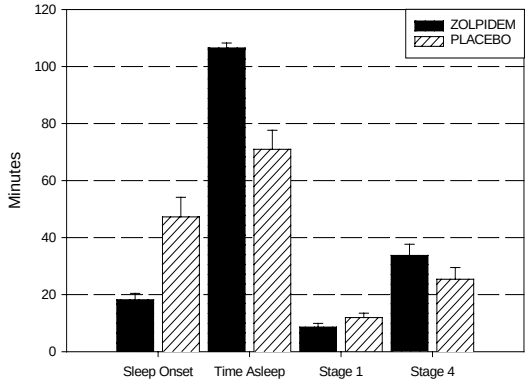

Figure 2. Effects of nap condition on sleep parameters.

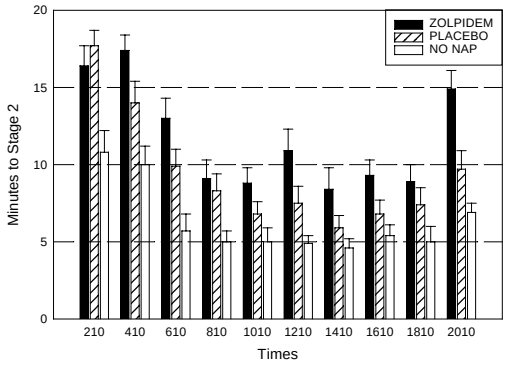

Figure 3. Latency to sleep onset on the RTSW for each napping condition.

MATB

MATB data were analyzed in a 2-way ANOVA for condition (Znap, Pnap, and Nonap) and time (0110, 0510, 0910, 1310, and 1710). The four tasks were analyzed separately.

Resource management. An examination of the mean deviation of units of fuel in tanks A and B from the target of 2500 revealed no significant main effects or interactions.

Communications. The ANOVA on RT and SDRT for correct responses and number of time-out errors indicated a condition-by-time interaction only on RT because of shorter RTs after both Znap and Nonap than Pnap at 1710 (see figure 4).

Systems monitoring. The ANOVA on RT, SDRT, and time-out errors to lights and dials indicated condition-by-time interactions on the RT for lights and dials and SDRT for lights. In each case, there were differences among the conditions only at 0910; the RTs

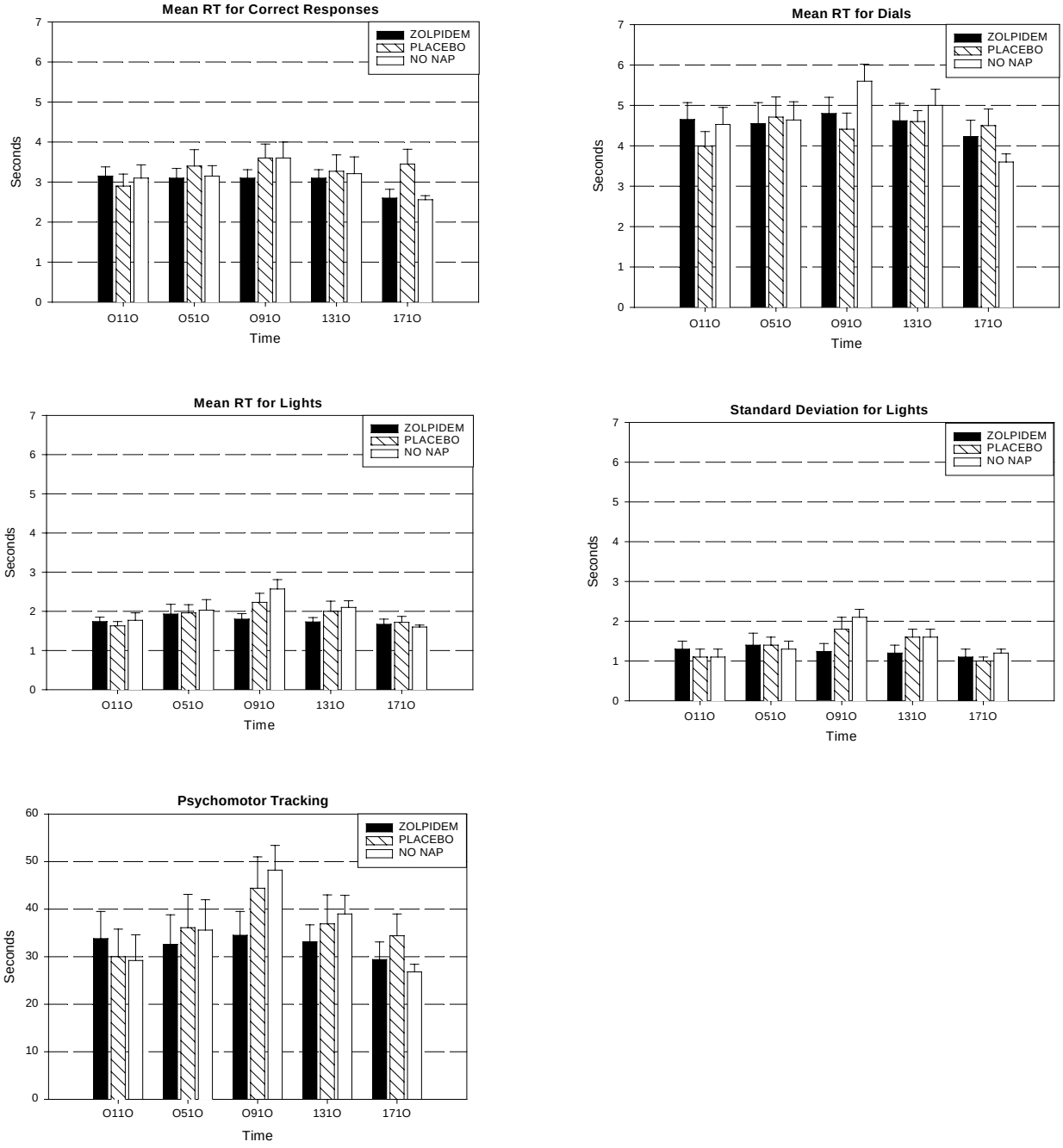

Figure 4. The effects of napping condition on performance of the MATB subtests.

for both lights and dials were faster after Znap than Nonap, the RT for dials was shorter after Pnap than Nonap, and the RT for lights was shorter after Znap than Pnap. SDRT for lights was smaller after Znap than either Pnap or Nonap (see figure 4). A condition main effect on RT for lights revealed a reduction in RT after Znap compared to Nonap.

Tracking. A condition-by-time interaction and a time main effect occurred on RMS errors. The interaction was due to differences among conditions only at 0910 where errors were smaller after Znap than Pnap or Nonap (see figure 4).

POMS

The ANOVA for condition (Znap, Pnap, and Nonap) and time (0100, 0300, 0500, 0700, 0900, 1100, 1300, 1500, 1700, and 1900) revealed an interaction only on vigor. Znap increased scores relative to Nonap at 0500 and 0700, while Pnap was better than Nonap only at 0700. At 1900, Pnap was better than both Znap and Nonap (see figure 5).

A condition main effect was found on the fatigue scale due to lower fatigue ratings under Znap than Nonap.

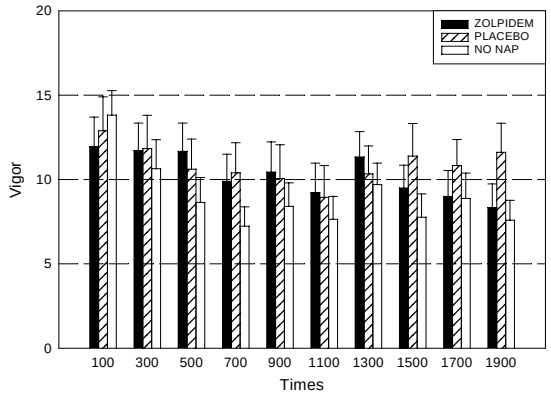

Figure 5. The effects of napping versus forced rest on POMS vigor ratings.

VAS

The VAS scores were analyzed in an ANOVA for condition (Znap, Pnap, and Nonap) and time (2300 and hourly from 0100 to 2000). There were condition-by-time interactions on alertness, energy, confidence, irritability, sleepiness, and talkativeness (see figure 6). Most resulted from inertia-related decrements immediately following the naps, which later gave way to nap-related improvements. VAS ratings were worse at 2300 after both Znap and Pnap compared to Nonap (alertness was also worse at 0100). However, beyond this time, naps attenuated the declines (except for confidence ratings which were unaffected late in the day). *Alertness* was higher after Znap than Nonap at 0400 and 0500, from 0700 to 1100, and at 2000; higher after Pnap than Nonap at 0400 and from 0700 to 1100; and higher after Znap than Pnap at 0500. *Energy* was higher after Znap than Nonap at 0400, 0500, 0700, and 0800; higher after Pnap than Nonap at 0400, 0700, and 0800; and higher after Znap than Pnap at 0500. *Irritability* was lower after Znap than Nonap from 0400 to 0800, but lower after Pnap only at 0700. Znap was significantly better than Pnap at 0500, 0600, and 0800. *Sleepiness* was reduced by Znap relative to Nonap from 0400 to 0800, at 1500, and from 1700 to 2000; sleepiness was reduced by Pnap relative to Nonap from 0400 to 0800, 1500, 1700, 1900, and 2000; and sleepiness was less after Znap than Pnap only at 2000. *Talkativeness* ratings were higher after both naps at 0500, and higher after Znap compared to Nonap at 0700 as well.

Condition main effects occurred on alertness, irritability, sleepiness, and talkativeness. On every scale, Znap was better than Nonap; Pnap was better than Nonap on sleepiness; and Znap was better than Pnap on irritability.

DISCUSSION

This evaluation of two types of 2-hour prophylactic naps (one induced with 10-mg zolpidem tartrate and the other a natural, or placebo, nap) during the final 23 hours of a 38-hour period of continuous wakefulness supported previous findings, which indicated both naps were superior to a forced-rest condition in terms of sustaining alertness. Comparisons between the zolpidem and placebo naps indicated the zolpidem nap was superior in several instances.

Sleep architecture of naps

The more rapid sleep onset and longer sleep duration in the zolpidem nap compared to the natural nap are consistent with other reports (Lorizio, Terzano, Parrino, Cesana, and Priore, 1990; Sanger, Perrault, Morel, Joly, and Zivkovic, 1987). Since subjects were provided with only 2 hours for each nap, zolpidem provided significantly more sleep than placebo. Subjects fell asleep almost twice as fast after zolpidem tartrate (24 minutes) than after placebo (46 minutes), and this no doubt contributed to the mild superiority of the zolpidem nap.

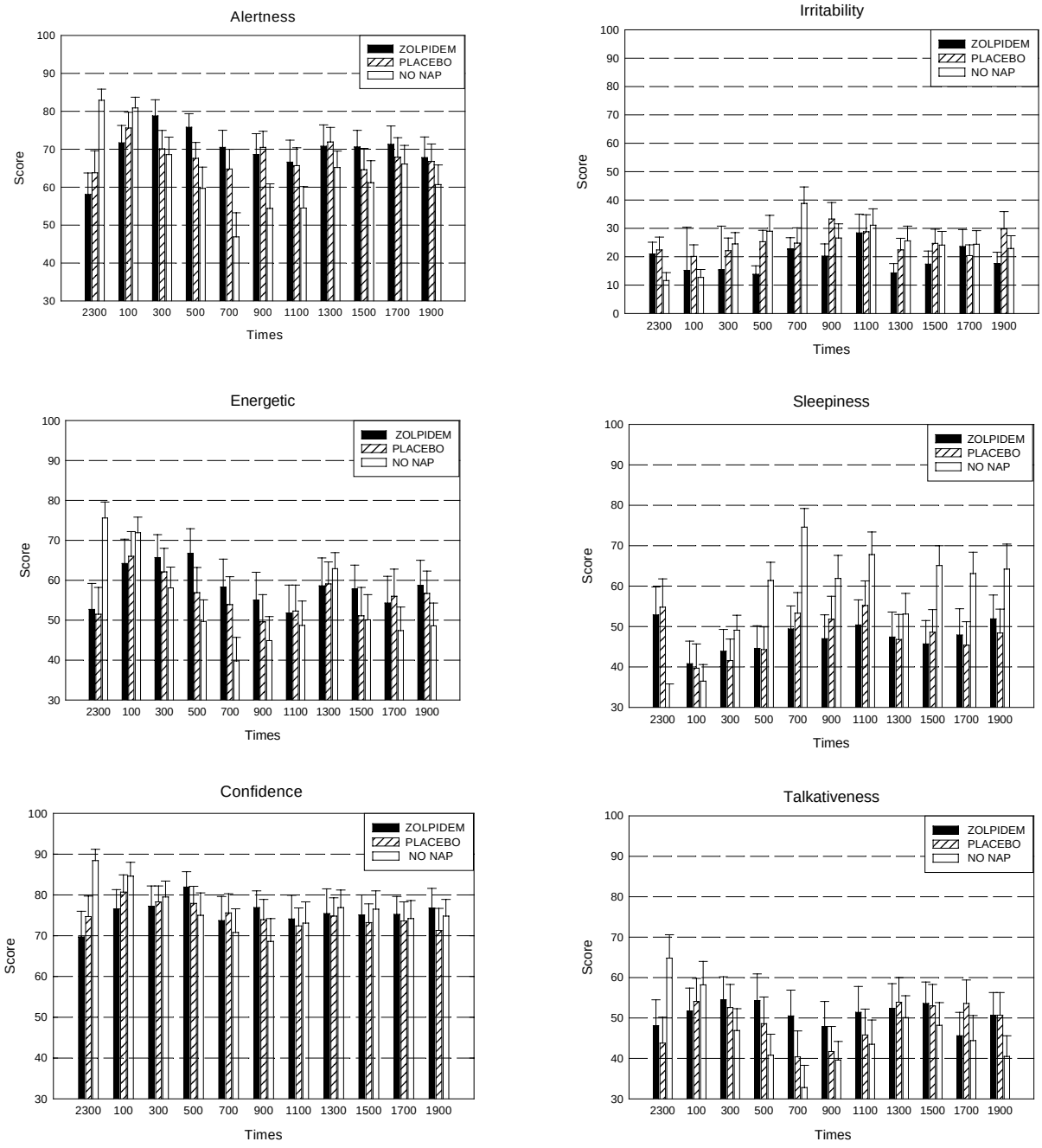

Figure 6. The effects of napping condition on VAS mood scales.

Sleepiness evaluations

Decrements in VAS alertness and energy ratings, coupled with increased irritability and sleepiness, were more pronounced after forced-rest than after one or both napping conditions, and the zolpidem nap often was superior to placebo. Of the 30 significant effects among conditions at various times, 97 percent were because the zolpidem-induced nap was better than forced rest; 63 percent were because the placebo nap was better than forced rest; and 20 percent were a result of better VAS ratings after the zolpidem nap than after the placebo nap.

VAS ratings in the present study were consistent with RTSWs, which indicated subjects could remain awake longer after the zolpidem nap than after the placebo nap or after rest only. It appears that the zolpidem naps were superior to placebo naps; alertness was greater after the zolpidem nap in comparison to forced rest during 100 percent of the RTSWs, greater after the placebo nap than after forced rest in 80 percent, and greater after the zolpidem nap than after the placebo nap in 50 percent of the RTSWs.

Unfortunately, the benefits from napping were not apparent immediately after subjects were awakened. VAS data collected at about 5 minutes after awakening from the 2-hour naps revealed that feelings of alertness, energy, confidence, and talkativeness were lower after both the zolpidem and placebo naps than after the forced-rest condition. In addition, ratings of irritability and sleepiness were higher after both naps than after forced rest. The mood effects disappeared by the time of the next VAS (about 2 hours after awakening from the naps), with the exception of the alertness decrement which persisted until, but not beyond, 0100. If measurements of mood had been obtained more frequently, there may have been increases in mood before 2 hours had lapsed. It is also unclear whether performance suffered along with mood during these times because the first test was not given until 2 hours after the nap; however, it has been suggested that mood disruptions caused by sleep inertia outlast performance decrements (Dinges et al., 1988). Postnap inertia was not more severe after zolpidem than placebo. Initially, there did appear to be a slight hangover effect on the ratings from several scales; however, none of these were statistically significant. The fact that the problems associated with sleep inertia immediately after the naps did not persist for more than 2 hours postnap was evident from an examination of the first RTSW (at 0210), which revealed greater alertness after both naps than after rest only.

Cognitive evaluation

Overall, performance suffered the most from sleep deprivation at the time at which mood and alertness decrements were most severe (in the midmorning hours). Prophylactic napping attenuated many of the problems, especially on tasks requiring vigilance and rapid responding. In addition, the zolpidem-induced nap tended to be superior to a natural nap.

Mood evaluation

Differences in vigor were most pronounced from 0500 to 0900 during the sleep deprivation period since these were the times when alertness suffered most under the no-nap condition. Differences in fatigue ratings occurred between the zolpidem nap and rest, with lower ratings after the zolpidem nap than after forced rest.

CONCLUSIONS

Zolpidem's rapid onset of action can be of significant benefit in situations where there is only a brief period available for sleep. When personnel have only 2 hours for a nap, zolpidem can maximize the effectiveness of that nap by rapidly inducing sleep. Although previous research indicates there are optimal times for napping, in the real world it may not be possible to schedule naps during these times. Work which must continue 24 hours a day with no breaks does not allow perfect scheduling of sleep breaks, so sleep must be taken when circumstances permit. When naps are possible, but the timing is less than optimal, zolpidem decreases the time to sleep onset and leads to more time asleep during a restricted nap period. However, to minimize problems, individuals who plan to use zolpidem should pretest themselves in a safe environment where performance demands are not eminent, and allow enough time from awakening to avoid sleep inertia. In addition, whether zolpidem-induced naps or natural naps are used, care must be taken to avoid the temporary problems associated with postnap sleep inertia by allowing personnel sufficient time to fully awaken from naps prior to returning to work. Research is planned to determine what countermeasures may be used to more quickly alleviate sleep inertia. Also, when zolpidem tartrate is used to initiate a 2-hour prophylactic nap, there may be some minor effects until approximately 5.5 hours postdose, although the practical impact of these effects is probably negligible.

DISCLAIMER

The opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army and/or the Department of Defense.

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Fatigue in Aviation Sustained Operations, the Utility of Napping, and the Problem of Sleep Inertia

John A. Caldwell, Ph.D., Brian F. Prazinko, B.S. and J. Lynn Caldwell, Ph.D.
U.S. Army Aeromedical Research Laboratory
P.O. Box 620577
Fort Rucker, AL 36362-0577, USA

E-mail: John.Caldwell@SE.AMEDD.army.mil

SUMMARY

Improperly managed aircrew fatigue can seriously degrade the performance, alertness, and safety of personnel in the operational environment. Fortunately, this danger can be minimized by the use of carefully planned napping strategies. Naps are effective because they are known to reduce the homeostatic drive for sleep. In a variety of settings, napping has been shown to produce several relatively long-lasting benefits. Unfortunately, there is a down side to this countermeasure in that personnel can suffer from several minutes of grogginess immediately after a nap has ended. This phenomenon is called sleep inertia. In operational contexts, the negative impact of sleep inertia must be weighed against the longer-lasting benefits of any napping strategy. If napping is to be implemented, specific steps can be taken to reduce the probability that sleep inertia will be severe and/or persistent.

BACKGROUND

The modern military mission requires that forces be able to deploy across multiple time zones, to virtually any destination in the world, with little or no advance notice. In addition, troops must be supported and maintained once they arrive on foreign soil. These requirements raise the necessity of frequent long-haul flight operations in which individual flights may last for 10-12 hours or even longer, especially since aerial refueling is an option. From an equipment/aircraft standpoint, such missions are certainly feasible, and because of system reliability and redundancy, there is little reason for concern over mishaps associated with mechanical or aircraft system failures. From the operator standpoint, however, performance problems represent a source of considerable concern because fatigue from extended cockpit duties can have serious adverse consequences (Dinges et al., 1996). In fact, a report by Ritter (1993) indicated that fatigue from sleep deprivation, circadian disruptions, and other factors is a major contributor to the cognitive and judgement errors made by aircrews.

Evidence of a fatigue problem in aviation

Proof that fatigue is an important aviation concern comes from a variety of sources, both civilian and military. In the civilian sector, the NASA Aviation Safety Reporting System (ASRS) suggests fatigue has been a factor in 21 percent of reported air incidents, and the U.S. National Transportation Safety Board has focused considerable attention on the problem of fatigue (Rosekind et al., 1999). Failure to effectively manage aircrew fatigue has led to such disasters as the crash of Korean Air flight 801 in which 228 people were killed (Hebert, 1999). In addition, fatigue was likely the culprit in the more recent mishap involving American Airlines flight 1420 in which 11 people died (Krause, 1999). Furthermore, fatigue was partially to blame in the 1985 near-crash of a China Airlines Boeing 747 (flight 006) and the crash of a DC-8 at Guantanamo Cuba Naval Base (Battelle Memorial Institute, 1998). From the standpoint of military aviation, Ramsey and McGlohn (1997) note that 25% of the Air Force's night tactical fighter Class A accidents were attributable to fatigue between 1974 and 1992, and 12.2% of the Navy's total Class A mishaps were a result of aircrew fatigue from 1977 to 1990. Furthermore, the U.S. Army Safety Center indicates that 4% of the Army's total mishaps (Class A, B, and C) from 1990 to 1999 were associated with aircrew fatigue (Army Safety Center, 2000).

Although many of these mishaps (particularly in the military sector) are not associated with long-haul flight operations, it is reasonable to postulate that the mere presence of fatigue-related problems in short-duration flights suggests an even larger-scale concern in long-haul settings. In fact, evidence from the civilian sector shows that long-haul, wide-body flight operations are associated with a loss rate that is approximately 3 times higher than the rate found in short and medium-range flights

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

(Caesar, 1986). Thus, alertness deficits stemming from prolonged flight duty require urgent attention.

Basic causes of aviator fatigue

During long-duration flights, fatigue/sleepiness stems from three major sources: 1) circadian disruptions associated with time-zone changes or rapid rotations to new work schedules; 2) cumulative sleep loss from extended periods on duty; and 3) the normally-occurring troughs in the circadian/sleep-wake rhythm (Rosekind et al., 1994). Each of these sources must be taken into account when developing an effective fatigue-management strategy.

Circadian disruptions from traveling across time zones (jet lag) result from a loss of synchronization between the body's internal physiological rhythms and the environmental light/dark cycle (Krueger, 1991). A similar difficulty occurs when personnel rotate among different work shifts within the same time zone (shift lag). The problem is that there are numerous internal processes that are normally locked together on a 24-hour schedule, and once disturbed, may require several days to fully readjust (Akerstedt, 1995). In the meantime, performance and alertness will be sub-optimal.

Cumulative sleep loss in aviators can stem from the intrusion of pre-mission duties into the normal sleep period, and the fact that by definition, late-afternoon or early-evening departures generally occur several hours past the crewmember's habitual bedtime. If the flight crew wakes at 0600 in the morning, and the flight does not depart until 1800 or later, this means that an 8- to 10-hour flight-duty period may not even start until after 12 hours of continuous wakefulness. Thus, by the scheduled landing time, the crew may have been awake for a continuous 22-24 hours, a period of sustained wakefulness known to produce performance decrements similar to those observed under the influence of alcohol (Dawson and Reid, 1997).

Troughs in the circadian/sleep-wake rhythm also can cause problems in long-haul flights despite the fact that they result from the body's normal daily internal rhythms. Alertness is known to decline at night as body temperature decreases and endogenous melatonin increases (Akerstedt, 1995). If a crew member is required to perform during this period (i.e., 0300-0500), judgement and response speed may be seriously impaired. This is particularly a problem for personnel traveling across multiple time zones because they are required to work when their bodies are normally asleep. Furthermore, they may experience sleep deprivation after arrival because they are attempting to sleep when their bodies are normally awake (Caldwell, 1999).

General fatigue countermeasures

There are countermeasures that can address these fatigue-related problems. Generally, they can be classified into one of two categories: preventive or operational (Rosekind, Gander, and Dinges, 1991). Preventive strategies focus on ensuring that personnel are well-rested prior to the start of each mission and/or that they have already adjusted to a new sleep/wake cycle prior to departing for a new time zone. Examples of specific interventions include: 1) minimizing pre-mission factors that interfere with restful sleep; 2) using hypnotics to promote sleep prior to deployments; 3) reducing the pre-mission time awake with prophylactic naps; or 4) using melatonin or bright lights to adjust the body's internal clock. Operational strategies focus on maintaining the alertness and performance of personnel after they have started the new mission (Rosekind et al., 1995). Examples of fatigue countermeasures that fall into this category are: 1) limiting the amount of continuous time on the flight deck between rest breaks; 2) taking advantage of strategic naps to bridge the gap between full blocks of sleep; and 3) administering stimulants (caffeine, dextroamphetamine, modafinil, etc.) to maintain performance despite sleep loss.

Napping

Of the countermeasures listed above, either normal sleep or napping should be considered first since only sleep can address one of the two primary factors underlying sleepiness/fatigue, namely the homeostatic sleep drive (Akerstedt, 1995). Since adequate continuous sleep is difficult to obtain in sustained operations, the present focus will center on napping. Although napping exerts little or no effect on the circadian influence over sleepiness and alertness, it can mitigate the general impact of fatigue during circadian low points by reducing the homeostatic sleep drive. Thus, a pilot who is suffering on a night flight because 1) he has been awake for 18 continuous hours and 2) he is at the trough of his daily circadian cycle will find significant relief from a nap because he has now, at least, reduced the impact of the continuous wakefulness (or the homeostatic drive for sleep).

Given the right circumstances, napping is easy to implement (unlike regimented crew schedules and duty limitations), is unencumbered by concerns about adverse long-term effects (unlike stimulant compounds), and has been shown to maintain or improve performance across a wide variety of settings (Dinges and Broughton, 1989). Angus, Pigeau, and Heslegrave (1992), for instance, found that even after 40 hours of sleep deprivation, a 2-hour nap prior to an additional night of sleep loss maintained performance at 70 percent of well-rested levels. More to the point for aviators, Rosekind et al.

(1994) has proven that cockpit naps can prevent many of the attention lapses and involuntary episodes of sleep intrusion (micro-events) encountered by crewmembers engaged in long-haul flight operations.

However, the use of napping as a fatigue remedy in operational settings has been slow to gain acceptance because of the problem of *sleep inertia*.

Sleep inertia

Sleep inertia defined. Sleep inertia is the name that has been given to the degraded vigilance, increased drowsiness, and diminished performance that occur right after awakening (Muzet et al., 1995). Kleitman (1963) observed that "immediately after getting up, irrespective of the hour, one is not at one's best." Sleep inertia is paradoxical because people immediately arising from sleep (when they should be most refreshed) consistently perform more poorly than they did hours earlier, just prior to going to bed (when they should have been most fatigued). This may present a serious concern when napping is proposed as an operational fatigue countermeasure, especially if skilled performance will be required immediately following the nap. However, this drawback must be compared to the longer-term performance problems that are known to occur when no napping (or longer sleep) is permitted. Before implementing an effective napping strategy for sustained operations, an understanding of the nature and characteristics of sleep inertia is necessary.

At the outset, it is important to note that generalizations about sleep inertia are sometimes difficult to make since similar measures appear to be affected inconsistently across different studies. For instance, Takahashi, Arito, and Fukuda (1999) found that sleep inertia suppressed subjective sleepiness/fatigue ratings for 2 hours after a nap, while Dinges (1990) saw no changes in subjective sleepiness ratings, even during severe sleep inertia. Sleep inertia also appears to have differential effects on different types of tasks (even within the same study). Ferrara, DeGennaro, and Bertini (2000), for instance, found that performance accuracy on a descending subtraction task was initially affected by sleep inertia but recovered after 30 minutes, whereas auditory tracking and finger tapping did not recover to baseline levels even after 75 minutes. Of course, differences among studies may simply be due to factors such as study design, the variables chosen for analysis, the samples on which the research was conducted, and differences within the same study could be due to other extraneous factors as well. But despite the discrepancies, it remains possible to make some basic assumptions about the problem of sleep inertia that may accompany naps in operational environments.

General effects of sleep inertia. In general, it should be expected that sleep inertia will affect both mood and cognitive performance, especially in highly demanding situations (such as prolonged periods of military sustained operations). In their review, Ferrara and DeGennaro (2000) concluded that tasks entailing high cognitive demands and those requiring a high degree of attention are affected more by sleep inertia than tasks involving simple motor skills. Furthermore, Bruck and Pisani (1999) revealed that complex decision-making ability may decline by as much as 49 percent within the first 3 minutes after an abrupt nighttime awakening. In addition, sleep inertia has been found to impact performance on a variety of other tasks.

Duration of sleep inertia. The precise duration of post-nap grogginess and disorientation depends on many factors; however, it appears that most sleep inertia dissipates 1-35 minutes after awakening. Akerstedt, Torsvall, and Gillberg's (1989) review of the issue cited one study that indicated sleep inertia persisted from 1-5 minutes, and another that suggested a more variable 5-35 minute range. Wilkinson and Stretton (1971) estimated the duration of sleep inertia to be 15 minutes, and Rosekind et al. (1995) generally concurred with this estimate, stating that most of the residual negative effects of napping appear to last no longer than 10-15 minutes. This is likewise consistent with the findings of Sallinen et al. (1998) who found that sleep inertia lasted only 10-15 minutes after subjects were aroused from 50-minute naps. Of course, there are other investigators who have estimated the duration of sleep inertia to be much longer (for example, Jewett et al., 1999; and Takahashi, Arito, and Fukuda, 1999 who suggested durations of 1-4 hours); but, these appear to be in the minority. Thus, for operational planners, it seems conservative to allow crewmembers at least 30 minutes from the time of awakening to the duty time for the purpose of ensuring that sleep inertia has fully dissipated.

Factors underlying sleep inertia. What are the factors that will determine the degree to which sleep inertia may affect performance in the operational environment? The answer to this question is not straightforward, but sleep inertia seems to be primarily a function of the stage of sleep from which someone is awakened. The phase of the circadian cycle may be important as well, although the research is less definitive on this point.

With regard to the importance of *sleep stage*, Wilkinson and Stretton (1971) concluded that awakenings from slow-wave sleep (SWS) produced more sleep inertia than awakenings from shallower stages. This was based on the finding that reaction time was worse when subjects were awakened in the earlier part of the night than the later part (because most SWS occurs during the first half of the night and most of rapid eye movement [REM] sleep occurs

during the second). These results were supported by Stones (1977), who found that performance on a memory task was worse when subjects were awakened from non-REM sleep than when awakened from REM sleep. Bonnet (1983) also showed that short- and long-term memory were worse after awakening from deep stage 4 sleep than after awakening from lighter stage 2 sleep. Additionally, Webb and Agnew (1964) found that reaction time and performance on a serial response task declined significantly from baseline levels when subjects were aroused from stage 4 sleep. These results concur with those of Ferrara et al. (2000), who found that large amounts of SWS rebound, during recovery from selective SWS deprivation, produced the greatest cognitive decrements associated with sleep inertia. Specifically, there were reported losses in both speed and accuracy, although the latter was affected most.

Differences in performance upon arousal from sleep also have been attributed to *circadian fluctuations*, although there is less agreement on this point than on the importance of sleep stage. Wilkinson and Stretton (1971) found that performance on a task requiring continuous concentration, as opposed to reaction time, was worse during the latter part of the night than during the earlier part of the night. The investigators attributed this difference to circadian fluctuations (performance during circadian troughs being worse than performance during circadian peaks). Circadian fluctuations were also found by Dinges, Orne, and Orne (1985) in a study in which people napped for 2 hours during circadian troughs and peaks over a 54-hour period. Performance immediately after awakening from naps during circadian troughs was impaired compared to performance immediately after awakening from naps during circadian peaks. However, in a study during which subjects were kept awake for 64 continuous hours with only brief naps (i.e., 20-minute naps) at 6-hour intervals, Naitoh, Kelly, and Babkoff (1993) failed to identify a specific circadian time at which sleep inertia was more or less severe. It may be that different conclusions on this issue are related to methodological factors, differences in the depth of sleep that is actually obtained at different times, or some other issue. Until this is resolved, the focus on minimizing sleep inertia probably should remain more on the effects of sleep stage (and sleep depth) than on other factors that are not presently well-understood.

Minimizing sleep inertia in operational settings

From an operational standpoint, it will not be possible to monitor the brain activity of personnel in order to ensure that they are not awakened from a strategic nap in the midst of SWS. Thus, other means should be used to minimize the possibility of such awakenings:

1) Avoiding high levels of sleep deprivation is one way to minimize the amount of SWS that will occur once personnel are afforded an opportunity to sleep. Bonnet (2000) reports that there are large increases in the percentage of time spent in SWS following total sleep deprivation; and Dinges, Orne, and Orne (1985) found that this increased SWS in naps (after sleep loss) was associated with greater postnap performance decrements. Thus, napping should be implemented before a significant sleep debt develops.

2) Placing naps at times when SWS is known to be reduced is another possibility. Generally speaking, young adults will spend most of the first third of their nightly sleep period in SWS, while the early morning phase consists primarily of REM sleep (Carskadon and Dement, 2000). Also, it has been found that naps taken later in the day contain more slow-wave activity than those taken earlier in the day (Borbely and Achermann, 2000). Thus, placing naps in the morning hours will reduce the possibility of awakening someone from SWS.

3) Keeping the nap period either short (less than 45 minutes) or allowing the nap to persist at least 110-120 minutes should reduce sleep inertia. The sleep pattern of a normal young adult during the first cycle of the night (nonsleep-deprived) will consist of 1-7 minutes of stage 1 sleep, followed by 10-25 minutes of stage 2 sleep, before reaching the deeper stage 3-4 sleep (Carskadon and Dement, 2000). Thus, assuming that it will take less than 10 minutes to initiate sleep in an operational setting (Rosekind et al., 1994), the occurrence of SWS should be minimized by allowing no more than a total of 45 minutes for the entire napping period. Alternatively, nap durations of 110-120 minutes should maximize the chances of awakening from either stage REM, stage 1, or stage 2 sleep (under normal, nonsleep-deprived conditions).

4) Finally, although debate remains about the importance of circadian factors in the management of sleep inertia, an effort should be made to avoid awakening personnel around the circadian trough (approximately 0300-0400). Although this is not a time when the amount of SWS would be expected to be high, it is a time when, generally speaking, cognitive/psychomotor performance and subjective sleepiness tend to be at their greatest (Van Dongen and Dinges, 2000).

SUMMARY AND CONCLUSIONS

It is well known that napping is an effective fatigue countermeasure for use in sustained operations. In fact, a real-world cockpit-napping

strategy developed by Rosekind et al. (1994) has already gained acceptance in both military and civilian long-haul flight operations. Strategic napping consistently attenuates the decrements in alertness and performance that are known to occur as a result of sustained operations without any sleep. However, the problem of sleep inertia is a point of concern when there is a high probability that personnel will be expected to perform demanding tasks immediately upon awakening.

To address this issue, operational planners must first weigh the difficulties associated with immediate, transient, nap-related decrements against the longer-term degradations that will no doubt occur in the presence of sustained continuous wakefulness (with no naps). If the benefits of naps appear to outweigh the drawbacks, every effort must be made to use napping strategies that are designed to minimize sleep inertia. In these situations, naps should be scheduled at intervals that will avoid the build-up of significant sleep debt, they should be placed in the morning as opposed to late at night, and their duration should be controlled so as to minimize the possibility of awakening personnel during slow-wave sleep.

DISCLAIMER

The opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army and/or the Department of Defense.

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Placebo-Controlled Studies of Sustaining the Alertness and Flight Performance of Aviators with Dexedrine®

J.A. Caldwell and K.K. Hall
U.S. Army Aeromedical Research Laboratory
P.O. Box 620577, Fort Rucker, AL 36362-0577, USA

E-mail: John.Caldwell@SE.AMEDD.army.mil

SUMMARY

Dextroamphetamine (Dexedrine®) is a stimulant capable of temporarily reversing many of the effects of sleep deprivation. This report substantiates the efficacy of Dexedrine for aviation sustained operations. Specifically, it is shown that this countermeasure maintains flight skills, psychological mood, and physiological activation in sleep-deprived pilots. Dexedrine's positive impact is not offset by marked disruptions in recovery sleep, although "lighter sleep" was noted after the drug than after placebo. It is concluded that Dexedrine is a viable remedy for fatigue in aviation sustained operations, but it is not a substitute for proper crew-rest scheduling. There is no replacement for adequate restful sleep.

INTRODUCTION

In part, because of advances in night vision technologies and improvements in the reliability of new aircraft, it has become highly feasible for aviation units to operate around the clock for days and weeks at a time. In fact, such sustained operations now are viewed as a tactical necessity on the modern battlefield. Unfortunately, this creates difficulties from a personnel standpoint because it is difficult to ensure that soldiers are "at their best" during each duty cycle. Lengthy work periods can produce significant levels of fatigue due to circadian disruptions and insufficient sleep.

Humans need periodic sleep for the restoration of both the body and the brain (Horne, 1978), and ignoring this fact leads to cognitive impairments, attentional lapses, and slower reaction times (Krueger, 1989). Sleep-deprived personnel can be expected to lose approximately 25 percent of their ability to perform useful mental work with each 24-hour period of sleep loss (Belenky et al., 1994).

To ensure that soldiers, and aviators in particular, can continue to perform despite significant sleep debt, it is essential that effective fatigue countermeasures be developed and refined. Unfortunately, several fatigue remedies have been proposed, but few have been more than marginally successful.

Policy/administrative countermeasures

Limiting the amount of time that personnel may work (or fly) during any given 24-hour period is one important way to reduce fatigue. Research suggests that long work hours tend to adversely affect workplace safety while reducing health. In fact, a three-fold increase in industrial accidents has been found to occur after 16-hour work shifts (Rosa, 1995). Night work is particularly problematic when combined with overtime hours. Along these lines, it should be noted that several well-known catastrophes such as Three Mile Island, Chernobyl, Exxon Valdez, and the space shuttle Challenger all began in the early morning with errors made by personnel who had been on duty for extended periods. Thus, it is worthwhile to place restrictions on duty cycles. Unfortunately, the implementation of such restrictions has been less than optimal, partially because mission demands continue to grow while personnel and budgetary resources dwindle. This has certainly been the case in the U.S. Army (Department of the Army, 1996). Often, there simply is no choice except to "get the mission accomplished" no matter how tired the crews may be. In addition, it is clear that crew endurance guidelines suffer from the same types of problems as hours-of-service regulations have in the civilian transportation industry—they do not adequately incorporate scientific knowledge on sleep and circadian physiology (Dinges, Graeber, Rosekind, Samel & Wegmann, 1996). A variety of factors other than "time on task" (such as circadian phase, prior sleep quality, time since last sleep period, etc.) are directly related to crew performance, and these must be addressed to optimize mission readiness.

Behavioral countermeasures

There are a variety of behavioral countermeasures that might be undertaken by individuals in an attempt to improve their alertness in fatiguing situations. These consist of ensuring a high

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

degree of physical fitness, engaging in physical exercise to attenuate drowsiness, or relying on naps to compensate for lost sleep. Unfortunately, napping is really the only one of these three strategies that actually works.

Physically-fit people are better able to withstand prolonged periods of physical work than those who are sedentary, but there is no evidence that fitness is able to stave off mental fatigue. In fact, Angus, Pigeau and Heslegrave (1992) found that highly fit individuals were no better at sustaining intense cognitive work than those who were less fit in situations where alertness was compromised by sleep-deprivation.

The usefulness of physical exercise is likewise doubtful. Brief periods of exercise have been shown to temporarily increase arousal in sleepy personnel (LeDuc, Caldwell, Ruyak, Prazinko, Gardner, Colon, Norman, Cruz, Jones, & Brock, 1998; Horne & Reyner, 1995; Angus et al., 1992), but the effects are too transient to be of much benefit to air crews working prolonged hours. Also, there is some evidence that intense exercise might actually produce an *increase* in sleepiness several minutes after the exercise session despite its initial tendency to boost performance.

Napping is the best "behavioral" fatigue countermeasure because sleep is the only antidote for sleep deprivation. Thus, in situations where some sleep (but not a full 8 hours) is possible, napping should be employed (Dinges & Broughton, 1989). Napping has proven extremely beneficial in aviation (Rosekind, Gander, Miller, Gregory, Smith, Weldon, Co, McNally & Lebacqz, 1994) and elsewhere (Stampi, 1992). Unfortunately, the implementation of this strategy in operational settings is often difficult because: 1) the environment is not conducive to sleep; 2) the schedules of personnel do not permit naps at appropriate times in the circadian cycle; and/or 3) unpredictable mission demands make it impossible to schedule proper napping periods.

Pharmacological countermeasures

When all else fails, stimulants are the best (and often the only) way to counter the effects of severe fatigue. Stimulants are effective and easy to use, and their feasibility is not dependent upon environmental manipulations or scheduling modifications. This explains why pharmacological compounds such as amphetamines have been used extensively in several military conflicts. Of course, there are other types of stimulants that are available as well (Akerstedt & Ficca, 1997); but to date, the amphetamines appear to offer the greatest potential for combating fatigue in sleep-deprived personnel.

The efficacy of dextroamphetamine (Dexedrine®) in particular has been well-established. In the field, Senechal (1988) reported the effective use of Dexedrine with EF-111A Raven jet crews during an Air Force strike on Libya in April of 1986, and Cornum (1992) indicated similar success sustaining the performance of F-15C pilots during combat air patrol missions in Operation Desert Shield/Storm. Emonson and Vanderbeek (1993) also reported that Air Force pilots effectively used dextroamphetamine during Operation Desert Storm. With Dexedrine, the aviators were better able to maintain acceptable performance during continuous and sustained missions without unwanted side effects.

In the Laboratory, the efficacy of Dexedrine has been established in several studies with sleep-deprived helicopter pilots. These studies, conducted at the U.S. Army Aeromedical Research Laboratory, have included three evaluations of Dexedrine® throughout 40 hours of continuous wakefulness and one throughout 64 hours sleep loss. Two of the 40-hour studies were conducted in a UH-60 helicopter flight simulator (Caldwell, Caldwell, Crowley & Jones, 1995; Caldwell, Caldwell & Crowley, 1997), and one 40-hour study was completed in an actual UH-60 aircraft (Caldwell & Caldwell, 1997a). The 64-hour study was performed in the simulator (Caldwell, Smythe, LeDuc & Caldwell 2000). Dexedrine was shown to be efficacious in terms of sustaining flight performance on a variety of precision "instrument" maneuvers despite severe levels of sleep deprivation. In fact, performance was maintained at or near baseline levels even after 50 hours of continuous wakefulness.

OBJECTIVE

The present report will present a unified summary of key findings from these previous investigations by combining multiple smaller data sets into larger-scale analyses. These analyses will focus on overall flight performance, electroencephalographic activity (EEG), subjective mood reports, and recovery-sleep data.

METHOD

Participants

Twenty-eight Army UH-60 helicopter pilots were tested. Their mean age was 29.6 years, and the mean amount of flight experience was 1,038 hours. Seven volunteers were female and 21 were male. All passed a medical prescreen to rule out significant illnesses of any type, sleep difficulties, allergic reactions to medications, etc., and all signed consent forms which fully disclosed any hazards associated with the experiments. Participants refrained from ingesting caffeinated products during the protocols.

Apparatus

UH-60 simulator. Simulator flights (performed in three of the four studies) were conducted in a specially-instrumented UH-60 simulator (CAE-Link Corporation, Model Trainer ASSY-2B38, Binghampton, NY) with computer-generated visuals, 6-degree-of-freedom motion base, and a multi-channel data acquisition system.

UH-60 aircraft. Aircraft flights (performed in one of the four studies) were conducted in a UH-60 helicopter (Sikorsky Aircraft, Stratford, CT) equipped with a computerized flight monitoring system. This system recorded the same aspects of pilot performance that were collected in the simulator studies.

Waking EEG. EEGs were recorded via Grass (Quincy, MA) E5SH electrodes (filled with SigmaGel electrolyte) from electrode site C_Z. Data were amplified and stored on a Cadwell Spectrum 32 (Kennewick, WA). The low and high filters were set at 0.53 and 20 Hz, respectively, and the 60 Hz notch filter was used.

Profile of Mood States (POMS). Mood was assessed with the POMS, a 65-item test which measures affect on six scales: 1) tension-anxiety, 2) depression-dejection, 3) anger-hostility, 4) vigor-activity, 5) fatigue-inertia, and 6) confusion-bewilderment (McNair, Lorr & Droppleman, 1981)

Polysomnographic evaluations. Sleep architecture during recovery sleep was examined using a Nihon Kohden electroencephalograph (model No. EEG-4321P, Irvine, CA). Data were recorded via Grass E5SH electrodes from C_3, C_4, O_1, and O_2 (referenced to contralateral mastoids). Electromyographic (EMG) and electrooculographic (EOG) data were recorded via SensorMedics electrodes placed under the chin (for EMG) and at the outer canthus of left and right eyes (for EOG). Time constants and high filter settings were: 0.3 sec. and 35 Hz for EEG, 5.0 sec. and 10 Hz for EOG, and 0.003 and 120 Hz for EMG.

Procedure

Volunteers arrived at the Laboratory on Sunday for prescreening and preparation. Training sessions were conducted at 0900, 1300, and 1700 on Monday (training day). On Tuesday (control) and Thursday (control), there were testing sessions at these times as well. On Wednesday (the deprivation day in the first cycle), and on Friday (the deprivation day in the second cycle), testing sessions occurred at 0100, 0500, 0900, 1300, and 1700. On these days, drug or placebo doses were administered at 0000, 0400, and 0800. At each dose time, subjects received 10 mg Dexedrine or matching placebo. The study was double blind and counterbalanced, and subjects were randomly assigned to a specific drug/placebo order upon arrival.

The two deprivation cycles (Tuesday/Wednesday and Thursday/Friday) were separated by an 8-hour recovery sleep. The deprivation cycles began at 0700 on the morning of one day and ended at 2300 on the night of the following day. Each deprivation cycle included eight testing sessions at the times noted above. Each session began with a 1-hour flight, continued with the EEG (approximately 20 minutes after the flight), and concluded with the POMS (approximately 1 hour and 20 minutes after each flight).

Flights. There were 14 maneuvers of the type typically flown in a UH-60 helicopter. Included were straight-and-level (SL) segments, left and right standard-rate turns (LSRTs and RSRTs), climbs, descents, and a left-descending turn (LDT). During each maneuver, subjects were required to maintain an airspeed of 120 knots, but specific targets for heading and altitudes changed from maneuver to maneuver. Subjects were instructed to make all turns at a standard rate of 3 degrees per second (or 20 degrees of roll angle) and to perform climbs and descents at a standard rate of 500 feet per minute.

Based on the data collected on each individual maneuver, scores ranging from 0-100 (with 100 reflecting near perfect accuracy) were calculated for a variety of measures. These scores, based upon the extent to which subjects deviated from ideal target values, expressed how well subjects maintained headings, altitudes, airspeeds, and other parameters. The scoring bands for each parameter are listed in the table. Individual parameter scores were averaged to produce one composite flight score for each iteration of each maneuver.

Table. Scoring parameters for flight data.

	Maximum deviation for scores of:					
Measure (units)	100.0	80.0	60.0	40.0	20.0	0.0
Heading (deg)	1.0	2.0	4.0	8.0	16.0	>16.0
Altitude (ft)	8.8	17.5	35.0	70.0	140.0	>140.0
Airspeed (knts)	1.3	2.5	5.0	10.0	20.0	>20.0
Slip (ball width)	0.0	0.1	0.2	0.4	0.8	>0.8
Roll (deg)	0.8	1.5	3.0	6.0	12.0	>12.0
Vert. Speed (ft/m)	10.0	20.0	40.0	80.0	160.0	>160.0
Turn Rate (deg/s)	3.0	5.0	10.0	20.0	40.0	>40.0

Waking EEGs. EEG sessions occurred approximately 20 minutes after the flights. In each session, data were collected under eyes open and eyes closed conditions, for 1.5-minutes per condition. Data were recorded from F_z, C_z, and P_z, referenced to linked mastoids (impedances were 5,000 ohms or less), but only the C_z data will be reported here because the results from the other electrodes were found to be redundant. For scoring the data, each EEG record was visually scanned for three relatively artifact-free 2.5-second epochs (per eyes-open and eyes-closed iteration). Based on these EEG epochs, absolute

power values expressed in millivolts squared were calculated for each of four frequency bands: delta (1.0-3.5Hz), theta (3.5-8.0 Hz), alpha (8.0-13.0 Hz) and beta (13.0-20.0 Hz). However, since theta activity is the most uniformly accepted EEG indication of significant fatigue from sleep deprivation, it will be the only EEG data included in the combined analysis.

POMS. The POMS was given approximately 1 hour after the EEG. Subjects indicated on a standardized form how well each of 65 mood adjectives described the way he/she was presently feeling. Six factors (mentioned previously) were derived via computerized or hand scoring.

Polysomnography. On each of the nights when sleep was allowed, subjects slept for approximately 8 hours while electrophysiological data (EEG, EOG and EMG) were recorded. Recordings were made at the beginning of the study (baseline) and following each deprivation cycle. Thus, there were 3 nights in which sleep architecture data were obtained for analysis (i.e., the baseline night, the Dexedrine recovery night, and the placebo recovery night). The sleep data from each of these nights were scored according to the rules set forth by Rechtschaffen & Kales (1968). Although several parameters were calculated, the percentages of time subjects spent in stages 1-4 and rapid eye movement (REM) sleep will be the only data reported here.

RESULTS

Flight Performance

Flight performance scores from the four studies were analyzed for differences under placebo versus Dexedrine across the baseline flights (at 0900, 1300, and 1700) and deprivation flights (0100, 0500, 0900, 1300 and 1700) averaged across the six types of maneuvers (SL, LSRT, RSRT, Climb, Descent, and LDT). Only drug-related main effects and interactions are presented here for the sake of brevity.

A 3-way interaction among study, drug, and session ($F(18.06,144.46)=2.07$, $p=.0097$) was due to larger drug-by-session differences in the simulator protocols than in the in-flight protocol. Follow-up analyses indicated that performance was better under Dexedrine than placebo at three sessions (0500, 0900, and 1700) in the 40-hour simulator protocol with males; at three sessions (0500, 0900, and 1300) in the 40-hour simulator protocol with females; and at four sessions (0500, 0900, 1300, and 1700) in the first 40 hours of the 64-hour simulator protocol. However, differences in the in-flight study were found only at 0900. There was a consistent 2-way interaction between drug and session ($F(6.02,144.46)=16.87$, $p<.0001$) as well (see figure 1). This resulted from the lack of any baseline differences followed by significantly better performance under Dexedrine than placebo at each of the deprivation sessions from 0500 to 1700 across all of the maneuvers flown ($p<.05$). There was a drug main effect ($F(1,24)=21.30$, $p=.0001$) which was attributable to better overall performance under Dexedrine than placebo.

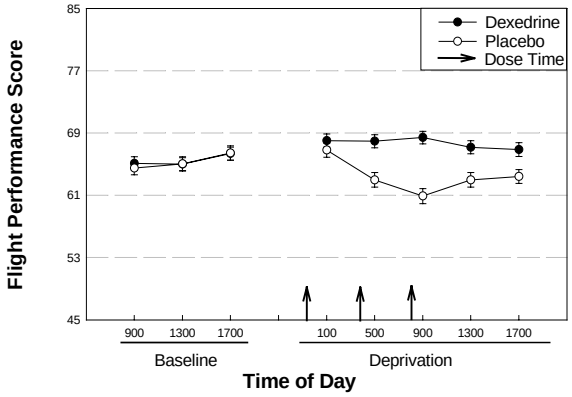

Figure 1. Performance was sustained at baseline levels by Dexedrine, but suffered under placebo.

EEG theta activity

Absolute power in the theta band from the eyes-open/eyes-closed EEG were analyzed with analyses of variance (ANOVAs) consisting of four factors: study (three simulator and one in-flight investigation), drug (placebo versus Dexedrine), session (1020, 1420, and 1820 on baseline; and 0220, 0620, 1020, 1420, and 1820 on the deprivation day), and eyes (eyes open/eyes closed).

There were two drug-related interactions. The first was a drug-by-eyes interaction ($F(1,23)=13.15$, $p=.0014$) that occurred because there were larger differences between Dexedrine and placebo under eyes-closed than eyes-open. The second was a drug-by-session interaction ($F(7,161)=5.83$, $p<.0001$) which was partially due to a peculiar reversal of EEG effects from the first baseline session compared to the last four deprivation sessions (see figure 2). There was more theta in the first Dexedrine baseline session than on the first placebo baseline session, but the opposite occurred at the sleep-deprivation times from 0620 to 1820 ($p<.05$).

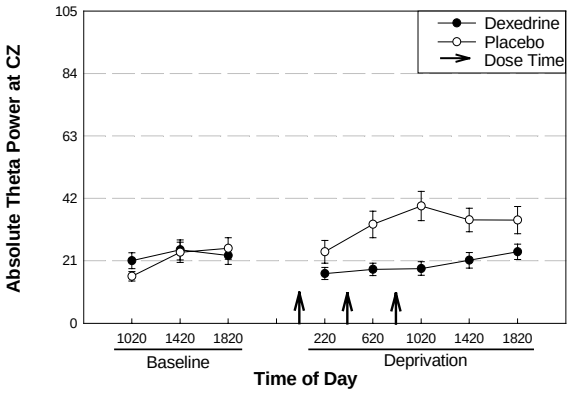

Figure 2. Fatigue-related increases in theta activity were significantly attenuated by Dexedrine.

POMS mood-disturbance data

Composite mood-disturbance scores under placebo and Dexedrine at four baseline times (1120, 1520, 1920, and 2340) and six deprivation times (0320, 0720, 1120, 1520, 1920, and 2340) from all four studies were analyzed with ANOVAs for study, drug, and time (or session). There was a drug-by-session interaction ($F(5.99,143.68)=16.05$, $p<.0001$) and a drug main effect ($F(1,24)=34.91$, $p<.0001$). Analysis of simple effects revealed no baseline differences, but that mood disturbance scores were significantly lower under the Dexedrine than the placebo condition at every deprivation time from 0335 to 2225 ($p<.05$). The drug main effect was consistent with what was found in the interaction. Overall mood disturbance scores were smaller under Dexedrine than placebo (the means were -7.8 and +5.4, respectively). Figure 3 graphically depicts the impact of drug and sleep loss on mood ratings.

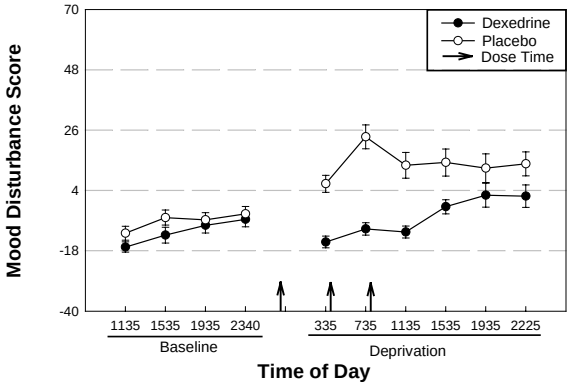

Figure 3. Negative mood scores, indicative of fatigue and confusion, were decreased by Dexedrine.

Polysomnographic data

The sleep-architecture data (percentage of time spent in each sleep stage) were analyzed in a two-way ANOVA for study (the four separate investigations) and night (baseline, Dexedrine recovery, and placebo recovery). This analysis revealed differences across the 3 days on stage 1 sleep ($F(2,48)=65.38$, $p<.0001$), stage 2 sleep ($F(2,48)=12.15$, $p=.0001$), stage 3 sleep ($F(2,48)=9.96$, $p=.0002$), stage 4 sleep ($F(2,48)=16.11$, $p<.0001$), and stage REM sleep ($F(2,48)=23.64$, $p<.0001$). Generally speaking, sleep was better after the deprivation cycles than during baseline. Also, sleep tended to be better after the placebo cycle than the Dexedrine cycle (i.e., less of stages 1 and 2 sleep and more of stage REM sleep after placebo).

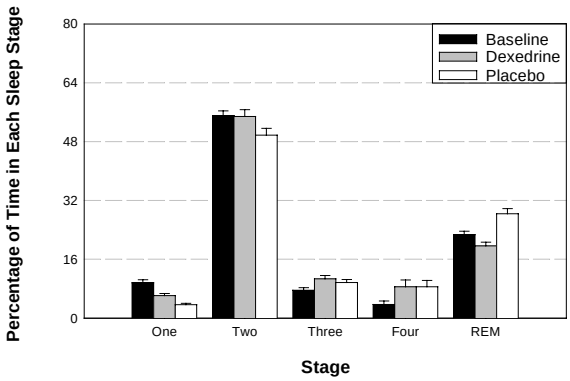

Figure 4. Sleep was slightly more shallow after the Dexedrine cycle than the placebo cycle. Also, there were numerous differences between the baseline night and the postdeprivation nights.

DISCUSSION

This investigation integrated the findings from four previous studies on the efficacy of Dexedrine for maintaining the performance and alertness of sleep-deprived pilots. The results supported earlier conclusions that prophylactic administration of repeated 10-mg doses effectively attenuates the impact of sleep loss on flight performance, mood, and physiological arousal when aviators are kept awake continuously for 40 hours. Effects were particularly noteworthy after 20 to 29 hours without sleep (between 0300 and 1200).

It is noteworthy that very similar patterns of results occurred with each of the four studies, a finding which suggests that data obtained from one group of pilots can be generalized to others despite small sample sizes. There was only one instance of a difference in the magnitude of the drug-related effects as a function of whether the subjects were participating in one study or the other. Although Dexedrine clearly sustained performance despite substantial sleep deprivation throughout all of the assessments, actual in-flight testing was less sensitive to the positive impact of the drug (and the negative impact of sleep loss) compared to simulator testing. As has been discussed elsewhere (Caldwell & Roberts, 2000), this probably resulted from increased

physiological activation in the aircraft versus the simulator (since the consequences of a mistake are more serious in the in-flight environment). Such an arousal increase tends to preserve performance under the placebo condition, making differences between placebo and Dexedrine smaller. Despite this difference in simulator versus in-flight performance, the general pattern of drug effects still indicated that Dexedrine attenuated the performance decline which occurred under placebo. Similar effects were observed in the physiological (EEG) and mood (POMS) data which showed that Dexedrine significantly reduced the adverse impact of sleep loss (regardless of whether the data were collected as part of the in-flight study or as part of the simulator research).

Examination of the overall flight data showed that performance declined substantially under placebo at four out of five deprivation sessions, while performance under Dexedrine did not. This finding, with short-interval 10-mg doses, extends those of Pigeau et al., (1995) who reported that widely spaced 20-mg doses were effective for attenuating initial performance declines and for recovering already-degraded performance.

The EEG data revealed that central-nervous-system (CNS) activation was affected similarly in that Dexedrine preserved EEG activity at more normal levels compared to placebo. Generally speaking, sleepiness and fatigue are known to accentuate the amount of slow-wave brain activity (Pigeau, et al., 1995), and increased theta activity has been associated with generalized performance decrements on cognitive tasks (Belyavin & Wright, 1987) with reduced speed of responding to incoming stimuli (Ogilvie & Simons, 1992). Thus, the fact that Dexedrine not only attenuated theta activity, but maintained theta at predeprivation levels, is a finding that coincides well with the flight-performance results.

POMS mood-disturbance scores revealed a reduction in negative reactions to sleep loss (such as increased anger, depression, fatigue, and confusion) under the Dexedrine treatment. Although there were some sleepiness-related deteriorations in mood under both drug and placebo, it was markedly smaller under Dexedrine. Such findings are consistent with those of Newhouse et al. (1989).

The sleep data from the first night of the study (baseline) and the recovery nights following the two deprivation cycles indicated that there was some cost associated with Dexedrine administration. Dexedrine decreased the restfulness of the recovery periods by increasing the amount of time that subjects spent in the lighter stages of sleep. Also, Dexedrine substantially reduced the amount of REM sleep relative to what was seen during baseline and the post-placebo recovery period. Whether the lighter sleep under Dexedrine would be of concern in actual field operations is difficult to know, but the size of the effects suggests that problems would be minimal as long as the sleep period was not restricted to less than 8 hours. The impact of altered REM sleep during recovery is unclear since the function of REM sleep is not fully understood (Lubin, Moses, Johnson, & Naitoh, 1974; Johnson, Naitoh, Moses, & Lubin, 1974). If REM sleep consolidates memory and/or restores mental resources, repeated use of Dexedrine might lead to a progressive deterioration of higher-level thought processes. However, it seems unlikely that this would rapidly manifest itself as long as 1 night of recovery sleep (8 hours in length) is allowed after 40 hours of continuous wakefulness (Caldwell & Caldwell, 1997b).

SUMMARY AND CONCLUSIONS

Dexedrine has for years been proven effective for maintaining the performance of fatigued people in non-aviation settings (Weiss & Laties, 1967). The present findings show that Dexedrine is likewise effective in sleep-deprived aviators, and that the effects seen in one sample of pilots generalize easily to others. Such results suggest that well-controlled administration of dextroamphetamine is an appropriate fatigue countermeasure for intense and unpredictable sustained operations. The results of the present analysis support an earlier contention by Cornum, Caldwell, & Cornum (1997) that well-controlled administration of amphetamine, restricted to short- to moderate-term circumstances in which heavily fatigued aviators must perform continuously, “may make the difference between a mission completed safely and effectively, and one that ends in disaster” (p 57). However, it must be re-emphasized that no stimulant can replace effective crew-rest scheduling or provide a substitute for restful, restorative sleep.

DISCLAIMER

The opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army and/or the Department of Defense.

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Substance éveillante : la caféine
(Wakening Substances: Caffeine)

Médecin en Chef Didier Lagarde*, Médecin Principal Bruno Sicard**
Dr Françoise Chauffard*, Médecin Principal Maurice Beaumont******

* Délégation Générale pour l'Armement
DGA/DSP/STTC/SH
26 bd Victor
00460 Armées, France

*** NESTEC Centre de recherche Nestlé
Vers-Chez- Les-Blanc 1000
Lausanne 26
Suisse

** Marine Nationale Antenne Programme
Etat Major
83800 Toulon
Naval, France

**** Institut de Médecine Aérospatiale
IMASSA BP 73
91223 Bretigny/Orge
France

Abstract :

Caffeine is the most widely used psychostimulant, whose acceptance, tolerance and side effects are well known. The development of a slow released (SRC) formulation optimizes caffeine as a fatigue and sleep deprivation counter-measure. Due to its pharmacokinetic properties (delayed T_{max} and reduced C_{max}), a single 300 mg SRC oral dose per day is effective to maintain alertness and performance, up to 45 hours in a total sleep deprivation situation. Compared to other psychostimulants like amphetamines or modafinil, slow released caffeine offers the best ratio effectiveness/tolerance-acceptance. Therefore SRC potential use in the military is wider than these "exotic" drugs, and could benefit to military personnel submitted to sustained or continuous operations.

1. Introduction.

1.1. Historique du café.

La caféine est le psychostimulant le plus consommé au monde, que ce soit sous forme de café ou de boissons de type sodas. Si le café n'a débarqué en Europe qu'au début du XVII° siècle, c'est au IX° et au XI° siècle que les médecins Perse Rhazès puis Avicenne mentionnent dans leurs écrits le café [1]. Une légende raconte qu'en 850 avant Jésus-Christ, au Yémen, un berger avait constaté que ses chèvres devenaient excitables lorsqu'elles mangeaient des baies rouges de caféier, le prieur d'un couvent voisin prescrivit alors une décoction de ces graines à ses moines pour maintenir leur éveil pendant les offices nocturnes. Ces effets stimulants du café sous forme de décoction sont rapportés par Dufour[2] dans son traité du café publié en 1693 : « l'effet du café est de tenir éveillées les personnes qui en ont pris »… « Villis, fameux Médecin d'Angleterre oppose le café aux remèdes Narcotiques ». Les mécanismes d'action du café sont encore imprécis, mais déjà avec Dufour apparaît la notion d'une substance spécifique contenue dans le café (pas encore identifiée comme la caféine), qui « maintiendrait les pores du cerveau ouverts, & donnent lieu à un passage continuel des esprits dans cette partie qui les fournit de même aux nerfs des yeux, des oreilles & autres organes des fonctions animales ». C'est cette substance spécifique appelée extrait spiritueux, qui est décrite en 1806 comme tonique, échauffante, très salutaire, sans abus, aux personnes d'une texture molle, lâche, humide… »[3]. Il faudra attendre 1820 pour que la caféine soit isolée pour la première fois par Runge et Von Giese.

Communication présentée lors du cycle de conférences RTO HFM sur « La gestion des rythmes veille/sommeil lors des opérations continues/soutenues », organisé à Fort Rucker, en Alabama aux Etats-Unis, les 17 et 18 juin 2002; à Varsovie, en Pologne, les 24 et 25 juin 2002; à Paris, en France, les 27 et 28 juin 2002, et éditée dans RTO-EN-016.

Le café n'a pas toujours été bien accepté dans les sociétés et les motivations de ses détracteurs étaient plus souvent religieuses, politiques ou commerciales qu'hygiéniques ou de santé publique. Il a été ainsi interdit par les musulmans de stricte observance puis par le pape Clément VIII. En 1674 en Angleterre une « Women Petition Against Coffee » était publiée pour obtenir la fermeture des « coffee houses » qui détournaient les maris du foyer familial. A Marseille les marchands de vin, obtinrent en 1679 la soutenance d'une thèse de médecine qui affirmait que le café était nocif aux Marseillais « dont l'esprit n'était déjà que trop subtil et le sang brûlé »[1].

1.2. Composition du café.

La composition du café est complexe, avec 4 % de sels minéraux (potassium, sodium et magnésium essentiellement), environ 50 % de glucides, 15 % de lipides, 10 % de protéines et acides aminés, des composés azotés non protéiques dont les bases xanthiques (caféine, théobromine et théophylline), des arômes et pigments et des vitamines. La teneur en caféine d'une tasse de café varie de 50 à 120 mg suivant l'espèce botanique (l'Arabica en contient moins que le Robusta) et le mode de préparation, 360 ml de soda type cola, en contient de 30 à 60 mg et une barre chocolatée environ 7 à 20 mg.

1.3. Consommation de café.

La consommation moyenne quotidienne de caféine aux USA est de 200 mg (2,4 mg / kg) chez les adultes dont 90 % sous forme de café [4]. Un enfant de 27 kg qui consommerait 3 cannettes de soda au cola et 3 barres de chocolat par jour absorberait ainsi 7,2 mg / kg de caféine. Des taux plasmatiques de caféine mesurés chez des personnels de santé, buveurs de café, étaient compris entre 1,2 et 9,7 mg / l [5]. La prise toutes les 8 heures d'une dose de 150 mg de caféine, entraîne un taux moyen plasmatique de 9 µg/ml après la 6° prise [6]. Il existe aussi des formes comprimés ou gélules contenant de 30 à 100 mg de caféine, parfois associée à d'autres composés pharmaceutiques, utilisées comme stimulant ou antalgique.

1.4. La caféine.

La caféine, qui est donc le principe actif du café, est très rapidement absorbée et diffuse dans les milieux liquides, les organes et le système nerveux où elle est détectée 5 minutes après l'ingestion. Le pic sanguin survient en 60 minutes environ (T_{max}). Le métabolisme hépatique de la caféine est dépendant du cytochrome P450. La demi-vie (T½) de la caféine est de 3 à 6 heures, plus courte chez les fumeurs et plus longue chez les femmes sous contraceptifs oraux et les femmes enceintes.

La caféine, aux doses usuelles, agit principalement par blocage des récepteurs à adénosine mais d'autres mécanismes sont probables pour expliquer certains effets comme l'amélioration de la résistance à l'effort [7] : ingérée avant un exercice d'endurance, la caféine retarde l'installation de la fatigue. Consommée 45 minutes avant un exercice à 50 % de la VO2max, à la dose de 3.3 mg/kg de poids corporel, elle améliore significativement les paramètres ventilatoires évalués en spiromètrie [8].

Sur le système nerveux central la caféine exerce un effet stimulant de la vigilance, anti-fatigue, diminuant les temps de réaction de certaines tâches [9]. Les effets sur l'humeur (tension, irritabilité…) sont aussi très dépendants des habitudes de consommation de café, de la sensibilité individuelle et de la dose absorbée. Lorist et al. montre que la fatigue est un paramètre décisif dans l'effet stimulant central de la caféine : comparés à des sujets reposés, les sujets privés de sommeil présentaient après la prise de 200 mg de caféine, des

améliorations significatives de leurs performances (temps de réaction), de leur éveil cortical et de leur humeur [10].

A doses équivalent à deux tasses de café, la caféine tend à augmenter la pression artérielle (5 à 10 mm Hg) et à réduire la fréquence cardiaque (via les réflexes barorécepteurs).

Elle induit une bronchodilatation chez l'asthmatique, moins patente toutefois qu'avec la théophylline. Comme la théophylline la caféine a un effet diurétique qui reste modeste [11]. L'administration d'une dose moyenne de 311 mg de caféine engendre dans les deux heures post ingestion une augmentation significative du volume urinaire de 29 % en moyenne [12].

Une consommation excessive peut être responsable de symptômes comprenant anxiété, tremblements, agitation, irritabilité, dépression, trémulations, tachypnée, tachycardie, palpitations, anorexie, troubles du sommeil et diverses plaintes somatiques : brûlure épigastrique, épisode diarrhéique [13]… Ces symptômes de surdosage ou d'intoxication à la caféine, regroupés sous le terme de caféinisme sans être un véritable syndrome, surviennent le plus souvent pour des consommations de caféine dépassant les 250 mg / jour. Dans une étude chez 4558 Australiens, Shirlow a modélisé le risque relatif pour des consommateurs moyens de café (240 mg / j), de présenter ces signes de caféinisme comparés à des non consommateurs [14]. Chez les hommes, le risque relatif était de 1,6 pour les palpitations, de 1,3 pour les tremblements et de 1,4 pour les insomnies. Ces risques relatifs étaient respectivement de 1,7, 1,5 et 1,4 chez les femmes.

Tout comme les effets stimulants de la caféine, l'incidence de ces effets indésirables est sujette à une très grande variabilité individuelle[15] et le développement d'une tolérance.

L'arrêt brutal de consommation de la caféine peut induire un syndrome de sevrage, marqué principalement par des céphalées survenant 12 à 24 heures après la dernière prise, d'intensité maximale vers 48 heures et durant au maximum une semaine [16]. Ces céphalées cèdent très rapidement à la reprise de la consommation de caféine. L'incidence (de 25 à 100 %) et la sévérité de ce syndrome de sevrage augmentent avec l'importance de la consommation habituelle de caféine [17].

2. Utilisation en milieu opérationnel de la caféine.

Les propriétés psychostimulantes de la caféine sont donc potentiellement intéressantes pour un usage lors de missions militaires. Lors d'opérations continues (activité opérationnelle avec des opportunités de sommeil qui peuvent être brèves et dispersées durant le jour ou la nuit) ou soutenues (activité opérationnelle sans opportunité de sommeil) [18] les militaires sont soumis à des privations de sommeil, une fatigue, qui peuvent retentir sur leurs performances. Ainsi lors du déploiement des chasseurs furtifs F-117A dans le conflit du Kosovo en 1999, les pilotes effectuaient des vols de 14 heures (avec 18 ravitaillements en vol) en décollant de l'état du Nouveau Mexique vers leur base en Italie [19]. Ces équipages étaient donc soumis à des vols longs, peu stimulants pour la vigilance, et au décalage horaire après avoir traversé 10 fuseaux. Pour les équipages de bombardiers B-1B, French rapporte des vols de 36 heures qui nécessitent une gestion difficile de la vigilance et du sommeil [20].

Du fait de sa tolérance et de sa large acceptation (pas de rejet culturel ou légal comme au XVII° siècle) l'utilisation de la caféine a déjà été recommandé lors de conflits récents, par l'US Navy par exemple [21], alors qu'il était dénoncé au XVIII° par Frédéric le Grand de Prusse qui déclarait que les batailles étaient gagnées par des soldats abreuvés de bière et non de café [1]. Ainsi dans l'US Navy une enquête menée sur le porte-avions USS Independence a été conduite en 1992, pendant l'opération Southern Watch contre L'Iraq : le café et la caféine en

comprimés étaient les 2 psychostimulants les plus consommés par les équipages des aéronefs pour maintenir leurs performances.

Le fait que la caféine soit aussi bien acceptée, car elle est considérée suivant sa forme soit comme un produit alimentaire soit comme un composé pharmacologique, son usage comme contre-mesure de la fatigue fait prendre moins de risques médico-légaux comme on pourrait en avoir avec des molécules plus exotiques ou plus controversées telles que le modafinil et les amphétamines. L'exemple de la controverse concernant l'utilisation des contre-mesures des armes chimiques dans la guerre contre l'Iraq en 1990, illustre les conséquences médico-légales et médiatiques de l'utilisation de produits dont les interactions et effets indésirables potentiels sont plus ou moins connus [22].

Dans l'US Air Force en 1995, la caféine était recommandée pour améliorer la vigilance, maintenir l'éveil et retarder la sensation de sommeil. Les médecins du personnel navigant étaient sensibilisés au risque de déshydratation lors de vols prolongés du fait des effets diurétiques du café. La caféine était interdite 6 heures avant l'heure du coucher et la forme comprimé n'était pas autorisée [23].

Dans une étude récente menée chez 12 marins, leurs performances de recherche visuelle en exercice de navigation étaient améliorées par la consommation de 250 mg de caféine [24].

Dans une étude simulant 52 heures d'opérations continues chez 140 sujets, l'efficacité de la caféine a été comparée aux siestes prophylactiques [25]. La prise répétée de faibles doses de caféine (150 à 300 mg) toutes les 6 heures associée à des siestes courtes et itératives étaient plus efficaces pour maintenir les performances psychomotrices, l'humeur et la vigilance que l'absence de sieste ou de fortes doses de caféine (400 mg, une fois par 24 heures). Les effets de la dose unique de 400 mg de caféine se dissipait après 6 heures.

De nombreuses expérimentations ont montré l'effet potentiellement bénéfique de la caféine comme contre mesure des effets de la fatigue, voire pour améliorer certaines performances physiques. Ainsi 8 militaires de l'US Army ont vu leurs performances, lors d'un test d'effort à 80 % de leur puissance maximale réalisé à 4300 m d'altitude, progresser de 54 % avec 4 mg/ kg de caféine [26].

Ainsi, l'utilisation conjointe de 375 mg de caféine et 75 mg d'éphédrine chez des militaires Canadiens soumis à une course de 3,2 km de type commando avec équipement complet de 11 kg, a permis d'améliorer significativement les temps de course par rapport à l'utilisation d'un placebo [27].

La caféine est donc potentiellement intéressante pour les militaires en opération soumis à des fatigues physiques, des privations de sommeil, des désynchronisations de leurs rythmes biologiques du fait de jet-lag lors des déploiements lointains rapides ou du fait des opérations souvent conduites de nuit. Toutefois la forme buvable de la caféine (café ou sodas) n'est pas toujours bien adaptée à un emploi sur le terrain, par ses effets diurétiques (pénalisants en aéronautique), et par la faible durée d'action. Des doses importantes, sous forme d'une prise unique massive ou de prises répétées peuvent enfin être responsables de caféinisme, ou surconsommation de café avec son cortège de symptômes désagréables pouvant gêner le militaire consommateur en opérations. Les formes alimentaires de la caféine, ne sont donc pas très bien adaptées comme contre mesure de la fatigue et des troubles de l'éveil en opérations. Les formes en comprimés existantes en facilitant les prises répétées, présentent toutefois le même profil pharmacocinétique que la caféine solution.

3. La caféine à libération prolongée.

Une forme de caféine en gélule, à libération prolongée (LP) a été développée et semble plus adaptée aux besoins des militaires que les formes en solutions aqueuses (café, soda) ou en comprimés, de caféine simple. Cette CLP a pour but d'obtenir un effet éveillant suffisamment prolongé pour ne nécessiter qu'une prise par jour, sans perturber le sommeil et donc présenter des taux plasmatiques inférieurs au seuil d'efficacité lors du coucher, et en limitant les effets indésirables par la réduction du pic plasmatique maximum.

Cette caféine LP (CLP), qui se présente sous la forme d'une gélule dosée à 300 mg, retarde ($p < 0.05$) le pic de concentration maximal de caféine dans le sang (T_{max}) et réduit ($p < 0.05$) le taux sanguin maximal (C_{max}) de caféine (table I), la demi-vie n'étant pas significativement différente. La figure 1 illustre ces différences de cinétique entre caféine LP et normale, lors d'une évaluation en double aveugle randomisée selon un plan croisé chez 10 volontaires sains caucasiens, âgés de 20 à 39 ans.

Dans les études d'évaluation de la caféine à libération prolongée aucun des sujets n'a rapporté de modification du volume des urines émises ou de la fréquence des mictions. L'excellente tolérance a été démontrée par son évaluation chez 100 militaires, de sexe masculin, qui ont été soumis à une prise unique de 2 gélules de CLP, soit 600 mg [28]. A 600 mg de CLP, le C_{max} plasmatique moyen était 10.3 µg/ml. Comparés à des sujets sous placebo le groupe qui a absorbé la CLP n'a pas présenté de différences pour la vigilance, l'humeur et la qualité du sommeil après la prise. Seules la latence d'endormissement était pénalisée ainsi que la sensation de calme. Il faut relativiser ces deux effets, de même que l'absence d'amélioration de la vigilance par le fait que les sujets n'étaient pas en situation de privation de sommeil.

En situation de privation de sommeil de 32 heures la tolérance de la CLP chez 24 (dont 12 femmes) sujets a été aussi bonne [29]. La prise de CLP était unique à la dose de 150, 300 ou 600 mg. Parmi les 8 sujets dans qui ont rapporté des effets indésirables bénins et spontanément résolutifs (céphalées, palpitations…) on note un ratio de 7 femmes pour un homme, qui tend à confirmer une sensibilité plus grande des femmes à la caféine, probablement liée au métabolisme différent. Le pic de concentration salivaire chez les femmes après la prise de 300 mg de CLP était plus élevé $C_{\text{max salivaire 300 mg CLP femme}} = 4.7$ µg/ml comparé à celui des sujets masculins $C_{\text{max salivaire 300 mg CLP homme}} = 2.4$ µg/ml, de même que la biodisponibilité (Area Under Curve AUC) $AUC_{\text{300 mg CLP femme}} = 77.6$ µg/ml.h pour $AUC_{\text{300 mg CLP homme}} = 30.6$ µg/ml.h , et la demi-vie (T ½ femme = 7.6 h, T ½ homme = 4.8 h). La concentration salivaire de caféine est corrélée avec la concentration plasmatique avec un ratio de 0.74 [30]

Tout comme la caféine simple les effets sur les performance de la CLP sont en effet plus patents quand les sujets sont fatigués, la CLP tend alors à restaurer des performances dégradées. Dans les deux études pré-citées en situation de privation de sommeil de 32 et 64 heures, les performances psychomotrices et la vigilance, étaient mesurées par une batterie de tests psychomoteurs la Standardized Test for Research with Environmental Stressors (STRES) Battery, des tests itératifs des latences d'endormissement (TILE) et un enregistrement en continu de l'activité par actimétrie qui mesure l'activité du poignet et représente un indice indirect du niveau d'éveil.

Dans l'expérience de privation de sommeil de 32 heures, les 12 hommes et 12 femmes ingéraient soit un placebo, soit 150, 300 ou 600 mg de CLP [31]. Par rapport aux conditions placebo, la prise de caféine chez ces sujets fatigués par la privation de sommeil a amélioré significativement les performances et la vigilance jusqu'à la fin des tests d'évaluation soit 13

heures après la prise. La dose de 300 mg de CLP représentait dans ces conditions la posologie optimale (efficace et pas d'effets indésirables).

En situation de privation de sommeil de 64 heures, 16 volontaires masculins ingéraient toutes les 12 heures soit un placebo, soit 300 mg de CLP. Pendant toute la durée de l'évaluation la latence d'endormissement (TILE) est plus longue sous CLP que sous placebo. Cet effet bénéfique sur la vigilance significatif à partir de la 19° heure, c'est à dire le milieu de la première nuit sans sommeil, est corroboré par les résultats de l'actimétrie. L'effet favorable de la CLP sur les performances psychomotrices ne se manifeste significativement qu'à partir de la 24° heure, c'est à dire quand apparaissent les dégradations de performance sous placebo. Ces résultats sont donc cohérents avec l'effet de contre-mesure de la fatigue de la caféine, plus patent que l'effet stimulant en dehors de toute dégradation préalable des performances [32]. Cet effet bénéfique sur les performances psychomotrices évaluées par la STRES Battery se maintient jusqu'à la 45° heure dans ces conditions. La figure 3 illustre ces résultats (pertes de contrôle en tracking) en situation de privation de sommeil et lors des sessions de récupération (R1 à R4) effectuées le lendemain (R1 et R2) et le surlendemain (R3 et R4) de l'évaluation [33]. Les effets bénéfiques de la CLP ne se sont pas accompagnés d'effets résiduels : la qualité du sommeil de la nuit de récupération en fin de privation de sommeil, n'a pas été altérée, et les performances en phase de récupération ne sont pas significativement différentes que sous placebo [34].

4. Applications militaires de la caféine à libération prolongée.

Les caractéristiques pharmacodynamiques de la CLP que nous venons d'exposer sont particulièrement adaptées aux contraintes des opérations militaires. Le fait que la CLP soit de la caféine et uniquement de la caféine, elle bénéfice de l'acceptance et de la tolérance liées à ce composé mondialement consommé, ce qui permet de la proposer en remplacement de certains psychotropes. Les amphétamines sont en effet des stimulants consommés en situation opérationnelle [35] et sont efficaces [36] mais leurs effets indésirables les réservent à un usage ponctuel et implique des risques médico-légaux. Le modafinil, aux propriétés eugrégoriques (maintien de la vigilance), lui aussi efficace [37], est aussi réservé à un usage exceptionnel : il est ainsi inclus dans les trousses de survie des pilotes militaires français afin de maintenir une vigilance parfois vitale en conditions de survie. Bien toléré cette molécule est toutefois d'un usage limité à certaines pathologies (narcolepsie) et est bien plus « exotique » qu'un produit dérivé de l'alimentation, la caféine.

La CLP pourrait aussi remplacer avantageusement certaines prises de caféine à doses fortes ou trop souvent répétées qui entraînent des effets de type caféinisme ou des effets diurétiques pénalisant dans certaines situations (aéronautique, quarts, veille postée…).

La CLP, c'est de la caféine, rien que de la caféine, mais de la caféine. Elle pourra donc tout comme de la caféine entraîner des signes de caféinisme même si sa cinétique lui assure une meilleure tolérance à dose égale, elle pourra aussi, comme la caféine induire un syndrome de sevrage en cas d'arrêt brutal de consommation. Dans les conditions de sevrage à la caféine, la CLP peut aussi être utilisée comme traitement pour des combattants habitués à consommer régulièrement du café et qui brutalement arrêtent leur consommation quand ils sont projetés sur le terrain. Tout comme la caféine, la CLP consommée avant de dormir pourra entraîner des perturbations de sommeil. Tout comme la caféine, la CLP sera d'autant plus efficace que les performances seront dégradées par la fatigue, la privation de sommeil ou la désynchronisation des rythmes biologiques.

Enfin la CLP ne présente pas les qualités organoleptiques de la caféine sous forme de boissons, et n'apportera jamais les effets sociologiques bénéfiques de la consommation de café en groupe.

5. Conclusions.

La caféine à libération prolongée, CLP, par ses propriétés cinétiques offre donc un champ d'application plus large que la caféine simple. Bien tolérée, elle est aussi mondialement connue et acceptée, et sa consommation ne pose donc pas de problèmes légaux. Les données épidémiologiques et pharmacodynamiques des autres psychostimulants potentiellement utilisables en milieu militaire n'égaleront jamais les données disponibles sur la caféine ; cette connaissance facilite la prescription et donc la sécurité d'emploi de la caféine. Efficace et bien tolérée à la dose de 300 mg la CLP est donc une alternative crédible aux autres psychostimulants auto-consommés par les militaires ou prescrits par leur autorité.

Table I : pharmacocinétique de la caféine à libération prolongée comparée à une solution aqueuse de caféine.
* = p < 0.05 ** = p< 0.001

Caféine 300 mg	C_{max} µg/ml plasma moy. ± s.d.	T_{max} h moy. ± s.d.	T ½ h moy. ± s.d.
Caféine solution aqueuse	5.5 ± 0.6	1.2 ± 0.5	5.4 ± 1.9
Caféine à libération prolongée	4.4 ± 0.8 *	4.1 ± 1.1 **	5.1 ± 1.9

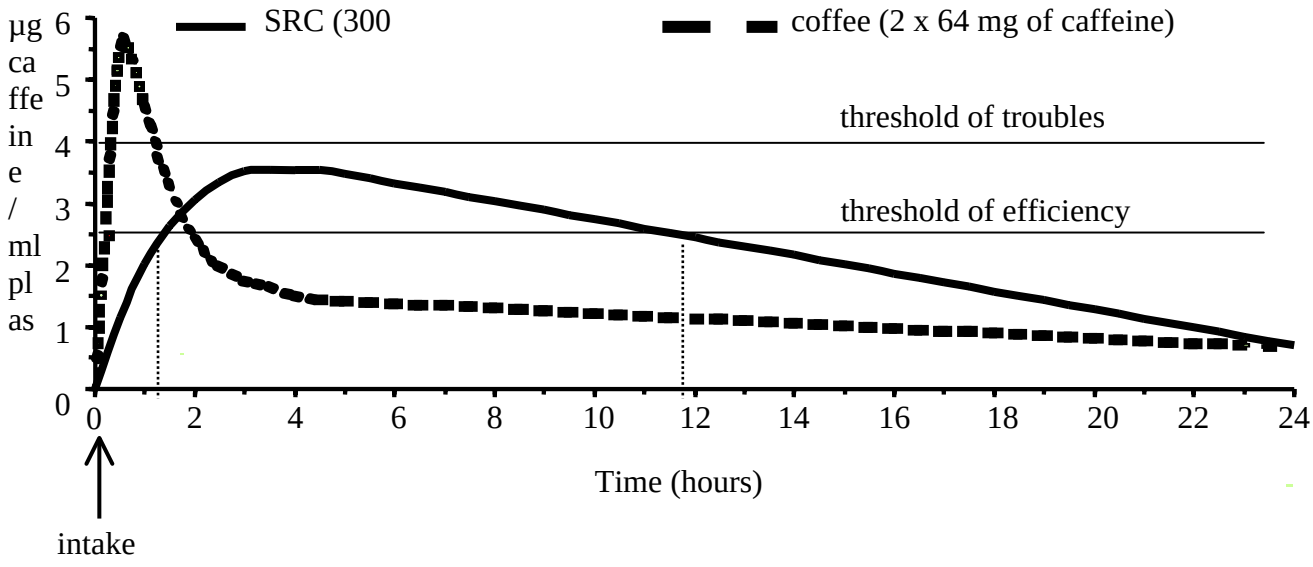


figure 2
Privation de sommeil de 32 h, pertes de contrôle au tracking

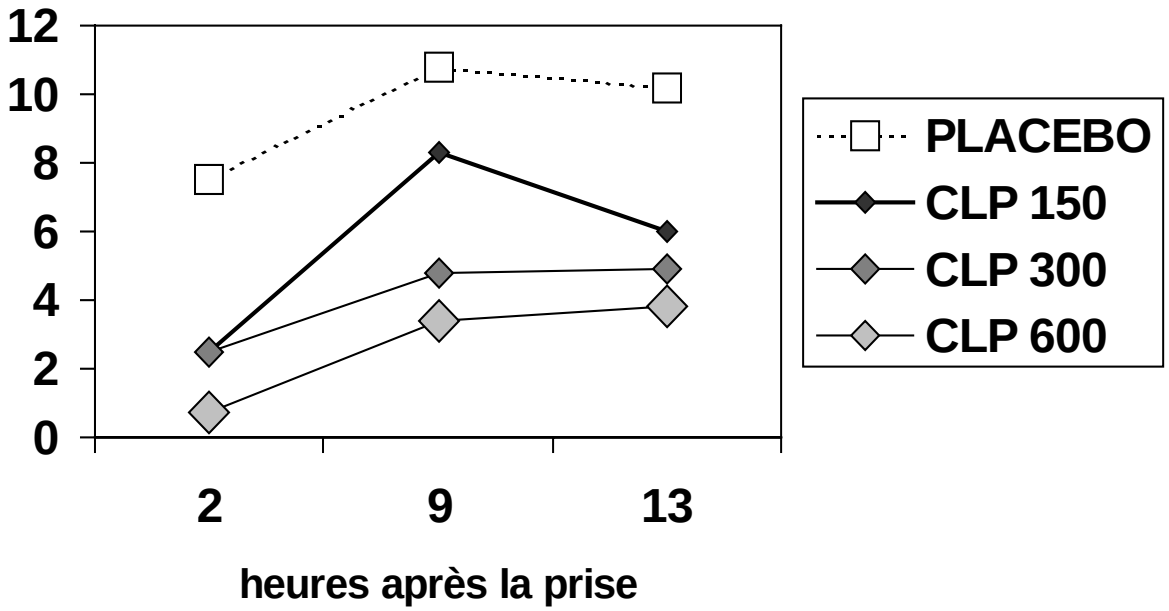
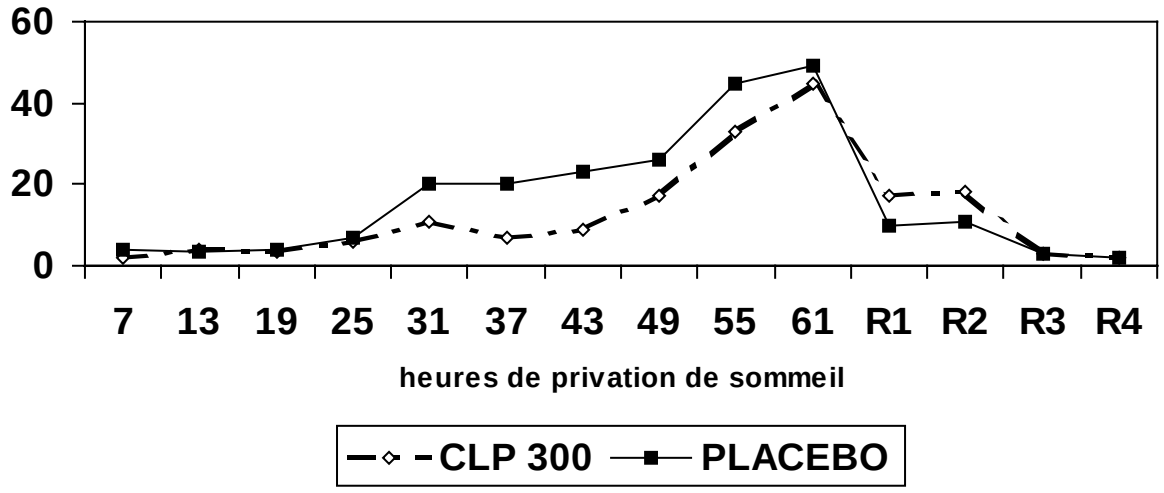


figure 3
Privation de sommeil de 64 h, pertes de contrôle au tracking



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Sleep Promoting Substances

Barbara M. Stone
QINETIQ Centre for Human Sciences
Cody Technology Park
A50 Building, Ively Road
Farnborough, Hampshire GU14 0LX
United Kingdom

SUMMARY

Adequate sleep is essential to the maintenance of alertness during continuous and sustained operations, and sleep promoting substances or hypnotics have been used successfully in support of demanding scenarios extending over many weeks. The rest periods during such operations are limited in duration and occur at intervals throughout the 24-hour cycle. There are many hypnotics now available, but the necessary profile is limited to a few drugs. These are temazepam (10-20mg), zolpidem (10mg) and brotizolam (0.125-0.25mg). With each drug there is evidence of efficacy and limited duration of actions with the dose range recommended. Melatonin (5mg) also possesses hypnotic activity, with efficacy during the day similar to 20mg temazepam. However, whereas the benzodiazepines and relate drugs possess hypnotic activity throughout the 24 hour cycle, it would appear that melatonin is only effective when the endogenous plasma levels of naturally occuring melatonin are low, and that ingestion at certain times of day may lead to sleep disturbance. The need to be aware of the constraints on the use of melatonin mitigates against its effectiveness in operations when missions will be required at all times of the day and night with rest periods scattered throughout the 24 hour cycle. As far as military operations are concerned the United Kingdom used the hypnotic temazepam (10-20mg) in Royal Air Force personnel during the South Atlantic campaign and during the liberation of Kuwait. It still remains the drug of choice for the Royal Air Force. The recent availability of ultra short acting hypnotics such as zaleplon (10mg) has raised the possibility of using hypnotics for shorter sleep periods than 6 hours.

INTRODUCTION

In the management of intensive and sustained operations the careful timing of work and rest periods may go a long way to avoid the decrements in performance associated with working for long periods which include duty overnight. However, after a few days it may be impossible to sustain sleep at acceptable quality. This may be due to a variety of reasons or to combinations of disturbing factors. For example, the time available for sleep may coincide with times which are not conducive to sleep, the presence of poor sleeping conditions or environmental factors associated with the mission such as noise, heat, uncomfortable posture may cause awakenings, or the overall stress and anxiety associate with the mission may disturb sleep. The greatest need for sleep is experienced between 2400 and 0600 and environmental clues normally encourage this. The quantity and quality of sleep are strongly dependent on the circadian phase; sleep taken during the day will be shorter and less recuperative than sleep taken at night. Although environmental factors during the day serve to accentuate this difference, even in rooms isolated from environmental factors sleep is less efficient during the day. It has been estimated that by the end of a week of night duty, the equivalent of at least one night's sleep may have been lost. While the duration of slow wave sleep is unchanged following night work, due to the duration of prior

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

wakefulness, stage 2 and REM sleep are reduced. When personnel are required to work at night this is at the lowest point in their circadian performance rhythm, strategies that can curtail the amount of sleep deprivation would be very beneficial. Work periods beginning in the early morning also lead to reduced sleep times. Because of the circadian peak in alertness it is difficult to retire to sleep early before an early shift. Lavie (1986) has described this time as the forbidden zone for sleep. Therefore even if the time is available for sleep if it is at the 'wrong' point in the circadian cycle personnel will be unable to take full advantage of the sleep opportunity. Working at night also exacerbates the age-related decline in sleep quality and quantity. Older subjects find it easier to adapt to early morning work periods. Commanders need to take these factors into account when planning work/rest schedules in operational conditions.

Under such circumstances it may be necessary to consider the use of hypnotic drugs to aid sleep. Some individuals appear to be able to sleep anywhere, at any time but others may be unable to gain any benefit from the time available for sleep. Adequate sleep is essential to the maintenance of alertness during continuous and sustained operations, and sleep promoting substances or hypnotics have been used successfully in support of demanding scenarios extending over many weeks.

HYPNOTICS

The largest class of hypnotics, the benzodiazepines, is known to speed sleep onset, reduce awakenings, and increase total sleep time in normal sleepers and those suffering from transient and chronic insomnia. In addition they may alter sleep architecture by delaying the appearance of rapid eye movement (REM) sleep, and increasing sleep spindles. The imadazopyridine zolpidem and the cycloprrolone zopiclone have similar effects on the EEG as benzodiazepines [Nicholson and Stone, 1983]. Zolpidem, however, may increase slow wave sleep, at least in young individuals and there is at least one report of a moderate increase in slow wave sleep with zopiclone [Nicholson and Stone, 1983]. Some have suggested that there is a special benefit to these newer nonbenzodiazepines. However the impact of drug induced changes in slow wave sleep is unknown. Essentially, the problems sleeping associated with sustained operations are characteristic of transient insomnia.

The rest periods during such operations are limited in duration and occur at intervals throughout the 24-hour cycle. It is, therefore, evident that the onset and duration of action of any hypnotic used in such circumstances are critical. Essentially these requirements demand a pharmacokinetic profile of rapid absorption and distribution / elimination rates which ensure freedom from residual effects within 6 hours of ingestion. There are many hypnotics now available, but the necessary profile is limited to a few drugs. These are temazepam (10-20mg), zolpidem (10mg) and brotizolam (0.125-0.25mg). With each drug there is also evidence of efficacy and limited duration of actions with the dose range recommended.

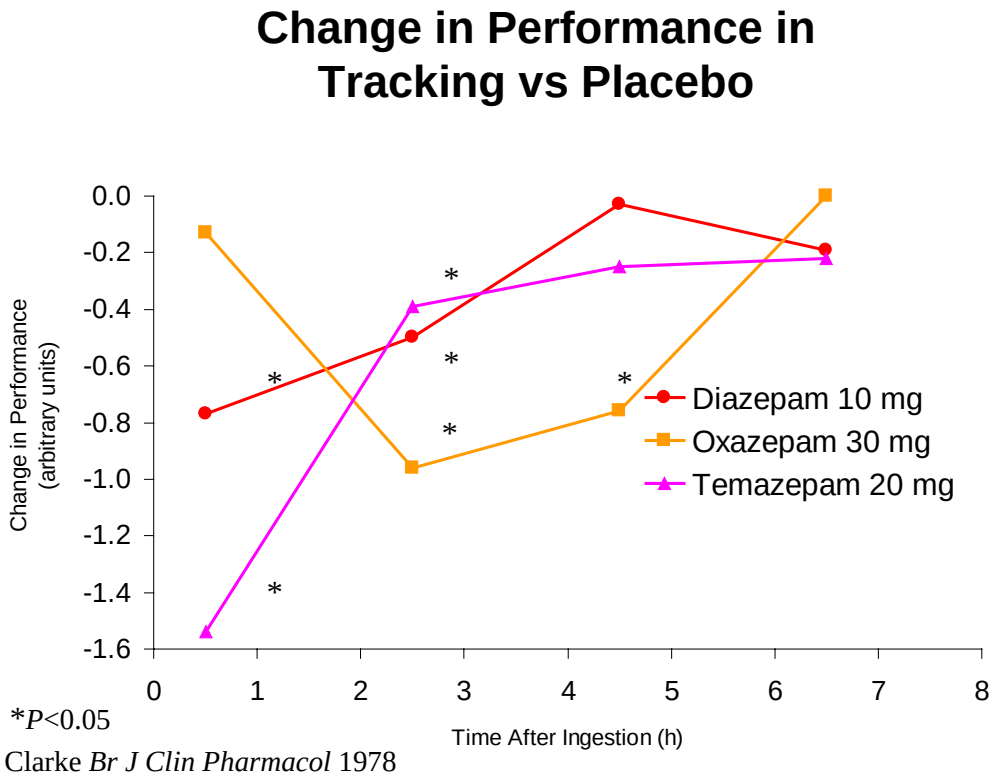
The key pharmacokinetic parameters of a range of hypnotic drugs are given below:

Key Pharmacokinetic Parameters

Therapeutic Agent	t_{max} (h)	$t_{½}$ (h)
Flurazepam	0.5–6	47–100*
Diazepam	0.5–2	20–80*
Temazepam	1–3	10–20
Oxazepam	2–3	4–20
Brotizolam	0.8–1.2	3–8
Zopiclone	1.0	3.5–6.5
Zolpidem	1.5	1.1–3.3
Zaleplon	1.0	0.9–1.1

*active metabolite

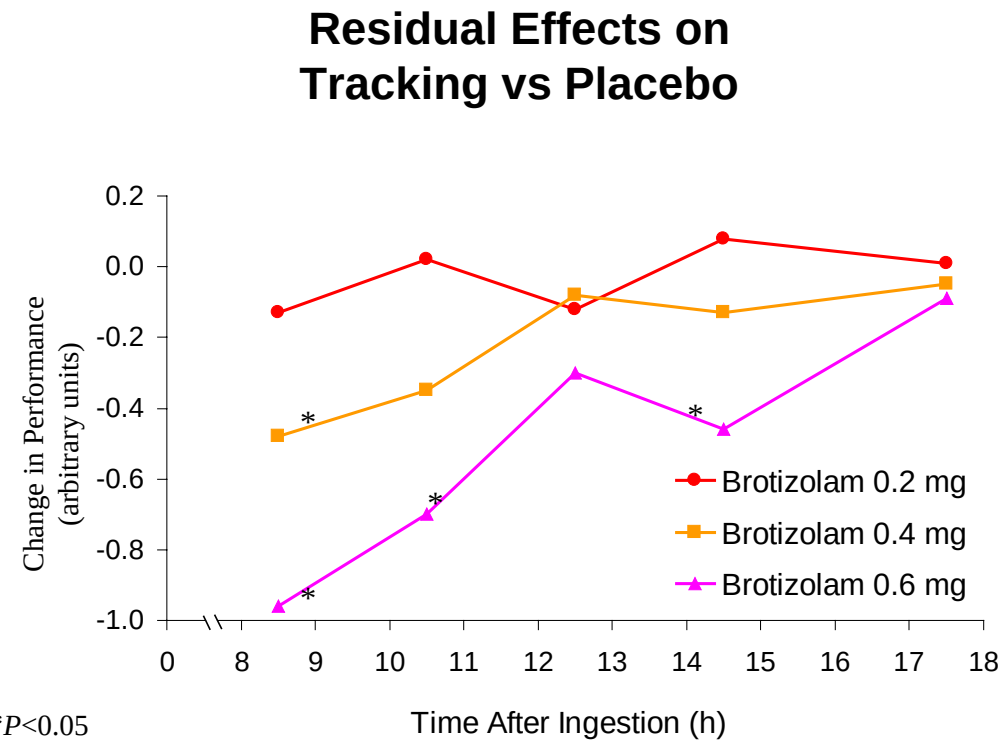
The mean elimination half-lives of brotizolam and zolpidem are around 5 h or less. Temazepam is a suitable hypnotic, which, although it has a longer half life, it has a relatively short duration of action due to the decrease in plasma levels as the drug is distributed from the central to the peripheral compartment. Zopiclone (3.75 – 7.5 mg) is also rapidly absorbed, but the activity of the recommended dose range extends beyond 6 hours. The limited duration of action of Temazepam, Brotizolam and Zolpidem has been shown in laboratory studies where a lack of residual effects on performance 6 hours after ingestion has been established. (Figures 1 & 2).



*P<0.05

Clarke *Br J Clin Pharmacol* 1978

Figure 1



*P<0.05

Nicholson *Br J Clin Pharmacol* 1980

Figure 2

RESEARCH AT MILITARY ESTABLISHMENTS

The main centres for research into the potential use of hypnotics in sustained and continuous operations has been in research establishments or universities which have been supported by the military. These studies not only tell us about the drugs considered for use by the military, but also the circumstances and scenarios for their use. Hypnotics are used for critical sleep periods and some studies have combined the use of a stimulant with a hypnotic.

Studies on the efficacy and residual effects of hypnotics were carried out at one of the establishments, which was partially subsumed into QinetiQ, the RAF Institute of Aviation Medicine. This research during the 1970s an 1980s examined a number of hypnotic drugs and temazepam was selected as the drug of choice for aircrew. A rapidly absorbed formulation and a dose of 10 or 20 mg provided useful hypnotic activity without residual effects on performance or mood. It was also useful at inducing sleep during the day and for these reasons it has been used by both military and civil aircrew in the United Kingdom for the last 20years. In particular it has been used in support of real intensive air operations [Baird et al, 1983, Nicholson et al 1985].

The Royal Australian Army Medical Corps have also carried out studies on the effects of temazepam (20mg) in relation to travel across time zones [Donaldson and Kennaway, 1991]. They reported a beneficial effect on sleep and alertness after transmeridian travel without adverse effects on performance. The rate of adjustment to the new time zone, however, was not increased.

The Italian Air Force has also carried out studies on temazepam [Porcu et al., 1997]. Temazepam (20mg) was studied in individuals who were subjected to a rapid shift of their sleep / wake cycle. It was effective at inducing and maintaining sleep during the day and was not associated with any carry over effects.

Temazepam has therefore been proved to be a useful drug for those attempting to sleep at times in the circadian cycle when sleep is difficult and also under the difficult sleeping conditions (heat, flies, noise etc.) encountered under operational conditions on Ascension Island. Unfortunately, in the United Kingdom at least, temazepam has become a drug of abuse, and for this reason its use is controlled. In spite of changes in formulation some abusers still use temazepam. and an alternative drug free of medico-legal constraints is desirable. In this context zolpidem would appear to be a useful drug. Studies in the United Kingdom have shown that in male subjects it is free of residual effects on performance and is also an effective sleep inducer during the day [Nicholson and Pascoe, 1986]. Studies in France have also evaluated zolpidem (10mg) for its residual effects on daytime wakefulness in navy fighter pilots [Sicard et al, 1993], and showed that in the absence of residual effects, zolpidem could be considered for operational use. The use of zolpidem (10mg) to aid napping has been studied by the US Army Aeromedical Research Laboratory, Fort Rucker [Caldwell and Caldwell, 1998]. The authors considered that post nap impairments could compromise performance under operational conditions. Other data which suggests that zolpidem may have residual effects on performance in some individuals will be discussed.

Zopiclone has been tested in the United Kingdom [Nicholson and Stone, 1983] and has been shown to have residual effects on performance 9h after ingestion at the 7.5 mg dose. This dose is therefore unsuitable for those who carry out skilled work.

OTHER DRUGS

Alcohol is often considered to be a sleep promoting substance, however, although it may initially promote sleep onset it also has detrimental effects on sleep [Stone, 1980]. The amino acid tryptophan has been reported to increase total sleep time on the first night after westward transmeridian travel [Spinweber, 1987] but its effects on sleep are generally considered to be unpredictable and limited [Nicholson et al., 1994].

A number of other drugs used to treat a range of medical conditions also possess sleep-inducing properties. The effects of H1 antihistamines on subjective and objective sleepiness and

performance have been widely studied. The first generation antihistamines are lipophilic, cross the blood-brain barrier with ease and have poor receptor selectivity, sedation is a major side effect of these drugs and their use in the treatment of allergy has been largely replaced by the second generation drugs which do not have these problems. In particular diphenhydramine is particularly sedating and for this reason is the main ingredient in many over-the counter sleeping aids. Promethazine is another sedating anthistamine, which is included in cold and influenza remedies, which are taken at night. Its sedating properties are also used when it is included as an active control in studies of the sedating and performance effects of a range of drugs. The use of these drugs in continuous and sustained operations has not been tested. However, it is possible that individuals who can buy them easily in their local pharmacist use them.
Many antidepressant drugs improve sleep. However, this sedation is accompanied by alteration of the sleep cycle such as suppression of REM sleep and performance deficits. Therefore, these drugs are considered unsuitable for use as a sleep inducer in those carrying out skilled work. Lithium improves nocturnal sleep but is also associated with cognitive deficits and is unsuitable for use in military personnel.

MELATONIN

Melatonin is a naturally occurring substance and for this reason has been considered to be a natural sleep inducing substance. There is therefore much interest concerning the activity of melatonin and how melatonin may be used to alleviate disturbances of circadian rhythmicity and insomnia, including the transient insomnia associated with transient and sustained operations. Experimental work on the possible adjustment of the circadian clock by melatonin is complicated by its sedative activity. This latter effect may improve sleep, thus alleviating the symptomatology of circadian desynchrony, and even normalising the sleep-wake cycle. Whether melatonin can induce a phase shift of circadian rhythms is an issue much debated [Arendt et al., 1997, Lewy and Sack, 1997, Sack and Lewy, 1997]. It may elicit a relatively weak phase shifting effect, but Cziesler [1997] has emphasised that this may be insufficient to induce a reliable entrainment. Any such effect with melatonin needs to be established by physiological parameters other than sleep and wakefulness.
Although sedative activity of melatonin has been demonstrated, its usefulness as a hypnotic is not clear. Indeed, Roth and Richardson, 1997 have emphasised that the majority of studies have evaluated only a single dose, or a limited dose range, and that there is a need for unambiguous information on its activity related to dose and to time of administration. Further, dose response data using electroencephalography is essential to an adequate understanding of its activity. Daytime ingestion of melatonin would appear to lead to reductions in sleep latencies [Dollins et al., 1994, Nave et al., 1996, Reid et al., 1996, Hughes and Badia, 1997], but studies on its activity around the normal time of sleep have failed to establish a useful clinical effect, except possibly in elderly insomniacs [Monti et al., 1999, Hughes et al., 1998, Dawson et al., 1998].
However, the usefulness of a hypnotic in the management of sleep disturbance associated with continuous and intensive operations would be dependent on it being effective at all times of the circadian cycle. It is in this context that a dose response study on the activity of melatonin when given in the early and late evening in healthy volunteers was carried out. The activity of melatonin was studied on nocturnal sleep (23:00-07:30) and on evening sleep (18:00-24:00), using electroencephalography, and was compared with that of a benzodiazepine (temazepam 20 mg) which is often used by individuals coping with irregular patterns of rest in critical situations. [Stone et al., 2000]
The subjects were healthy male volunteers free of the use of medication. They gave informed consent to take part in the experiment that was approved by the local Ethics Committee. In the nocturnal experiment the subjects were eight males aged 20 to 30 (mean 23.4) years weighing between 63 and 100 (mean 77) kg, and in the evening experiment the subjects were six males

aged 21 to 31 (mean 26.5) years weighing between 69 and 89 (mean 77.3) kg. One subject participated in both experiments.
During the evening preceding the day of each experiment the subjects retired at their normal bedtime and consumed no more than two units of alcohol. In the experiment on nocturnal sleep, caffeinated beverages were avoided from midday, and in the experiment on early evening sleep, subjects abstained from caffeine throughout the day. The order of drug ingestion in both experiments was based upon a Latin Square design. Medication was identical in appearance and the experiments were double-blind.
Experiment I: Each subject reported to the laboratory on eight occasions, at intervals of at least one week, and ingested at 23:30, on separate occasions, melatonin (0.1, 0.5, 1.0, 5.0 and 10 mg), 20 mg temazepam (active control) and, on two occasions, placebo. An identical performance test session of 8-min duration was carried out before and after each sleep period (23:30-07:30).
Experiment II: Each subject reported to the laboratory on six occasions, at intervals of at least one week, and ingested at 18:00, on separate occasions, melatonin (0.5, 1.0, 5.0 and 10 mg), 20 mg temazepam (active control) and one placebo. A performance test session of 4 min duration was carried out after each sleep period (18:00-00:00).

Sleep and body temperature
Electroencephalography: The subjects slept in single light-proofed, sound attenuated and temperature controlled (18±2^{o}C) rooms. Standard techniques for recording and analysing sleep were used [Rechtschaffen and Kales, 1968]. Various measures were derived from the data for subsequent statistical analysis.
Subjective assessments: Subjective assessments of sleep were completed 15 min after rising. Subjects also estimated the time to sleep onset and the sleep duration. The Stanford Sleepiness Scale [Hoddes et al., 1973] was completed prior to and after each sleep period.

Performance
Subjects were well trained on all performance tasks and were observed during the tasks by means of closed circuit television. In the experiment on nocturnal sleep, tests were presented at 23:00 (0.5h before drug ingestion) and at 08:00 (8.5h after drug ingestion) in the following order: digit symbol substitution (DSS), letter memory recall, picture memory recall. During each session, mood and well being were assessed using a series of twelve 100 mm visual analogue scales [Nicholson et al.,1984]. In the experiment on early evening sleep, DSS only was measured at 00:30, i.e. 6.5h after drug ingestion.

Melatonin onset
Endogenous dim light melatonin onsets (DLMO) were determined on completion of the nocturnal sleep experiment. The subjects remained in constant dim light (<8 lux) in an isolation unit from 17:00 to 03:00 and produced saliva samples at half hourly intervals. Salivary melatonin levels were determined by radioimmunoassay [English et al., 1993] and the dim light melatonin onset was calculated as the time at which melatonin levels reached twice the limit of detection of the assay (1.3 pg/ml). Immediately after providing each saliva sample, subjects were required to rate their fatigue level against 10 separate criteria on the Modified Samn-Perelli (MSP) checklist [Samn and Perelli, 1982]. From these ratings, a score in the range 0 (extremely fatigued) to 20 (extremely alert) was calculated.

Statistical analysis
An equation of the form: temperature = a + b * exp [c * time] was fitted to each subject's temperature data recorded during nocturnal sleep for each drug, and the values of a, b and c were estimated using a least squares fit. These three coefficients were analysed by ANOVA using a one factor model (drug) against subjects. A similar method was used for the temperature data recorded during early evening sleep, and the two coefficients (slope and intercept) were analysed

by ANOVA. The temperature data from both experiments, recorded at minute intervals, was meaned over 30 min intervals from lights out and analysed by ANOVA.

Night time sleep: One dose of melatonin (5 mg) reduced the duration of stage 3 in the first 100 min of sleep ($p<0.05$), though analysis of mean values for melatonin failed to reveal any change with melatonin compared with placebo in any sleep measure. Temazepam increased stage 2 sleep (duration and percentage in the first 6h and over the whole night; $p<0.01$), and duration in the first 100 min periods of sleep (from 59.1 min after placebo to 74.6 min after temazepam; $p<0.05$) and third 100 min (from 53.8 min after placebo to 68.3 min after temazepam; $p<0.01$). The latency to rapid eye movement (REM) sleep was also increased ($p<0.05$) compared with placebo. With temazepam there was a reduction in total and percentage of stages 0 and 1 combined, both in the first 6h of sleep and over the whole night (compared with placebo and the mean of the melatonin doses $p<0.01$).

Subjective measures: No difference was found between drug treatments in subjective assessments of sleep onset, sleep duration, sleep quality, alertness or mood. One subject reported vivid dreams and many awakenings with 0.5 mg melatonin, and sleep disturbance with early morning awakening with 1 mg melatonin. Another subject reported feeling "foggy" after 1 mg melatonin.

Temperature and performance: Body temperature during nocturnal sleep with 0.1 mg melatonin (36.18^{o}C, $p<0.05$) was lower than placebo (36.43 ^{o}C) 6.5 to 7h after lights out, but no other changes in body temperature with melatonin, either related to dose or time, were detected. With temazepam, body temperature during nocturnal sleep was reduced 4.5 to 5h (36.12 ^{o}C, $p<0.05$), 5 to 5.5h (36.11 ^{o}C, $p<0.01$) 5.5 to 6h (36.14 ^{o}C, $p<0.01$), 6 to 6.5h (36.18 ^{o}C, $p<0.05$) after lights out, compared with placebo (36.35, 36.38, 36.43, 36.43 ^{o}C, respectively). There were no changes in performance after the nocturnal and early evening sleep periods with melatonin or temazepam.

Melatonin onset: The endogenous dim light melatonin onset of all eight subjects occurred between 20:40 and 23:15. The mean time of melatonin onset was 22:02. Mild fatigue was reported on the Sam-Perelli fatigue checklist from 21:30h.

Early evening sleep

Objective measures: Melatonin increased total sleep time, sleep efficiency, the total duration of stage 2 sleep ($p<0.001$, all doses), the duration of stage 2 sleep in the second (0.5 mg, $p<0.01$; 1 mg, $p<0.05$; 10 mg, $p<0.001$) and third (0.5, 5 and 10 mg, $p<0.001$; 1 mg, $p<0.05$) 100 min interval of sleep. It also increased the percentage of stage 2 sleep (two lower doses, $p<0.01$; 5 mg, $p<0.05$; 10 mg $p<0.001$). Melatonin increased the number of REM periods (0.5 mg, $p<0.05$; 1 to 10 mg, $p<0.001$), the duration of REM sleep in the third 100 min interval of sleep (1 mg, $p<0.05$), increased the number of stage shifts (0.5 mg, $p<0.05$; 10 mg, $p<0.01$), and the percentage of wakefulness ($p<0.05$, all doses).. Melatonin (5 mg) increased the duration of stage 3 sleep (16.3 min) in the second 100 min interval of sleep, compared with placebo (4.7 min; $p<0.05$), and increased the total duration of stage 1 sleep and the duration of stage 1 sleep in the second 100 min interval of sleep ($p<0.05$). Melatonin (10 mg) increased wakefulness in the first 100 min interval of sleep, compared with temazepam ($p<0.01$).

Temazepam (20 mg) increased total sleep time and sleep efficiency ($p<0.001$). It also increased the number of stage shifts ($p<0.05$), reduced wakefulness (total duration, $p<0.05$ and percentage, $p<0.001$), increased stage 2 sleep (total duration, percentage, and duration in the third 100 min of sleep, $p<0.001$) and increased the duration of slow wave sleep ($p<0.05$).

Subjective measures: Melatonin, improved subjective sleep quality (0.5 to 5 mg doses, $p<0.001$; 10 mg, $p<0.01$) and reduced alertness following sleep (0.5 and 5 mg doses, $p<0.01$; 1 and 10 mg doses, $p<0.05$). The two lower doses of melatonin also increased the subjects' perceived requirement for sleep after the sleep period (0.5 mg, $p<0.05$, 1 mg, $p<0.01$). Temazepam (20 mg) reduced sleep onset latency ($p<0.05$), improved sleep quality ($p<0.001$), and reduced alertness following sleep ($p<0.001$). Subjects reported that sleep quality was better after temazepam than melatonin ($p<0.05$ compared with 0.5, 1, 5 mg; $p<0.01$ compared with 10 mg melatonin).

Temperature and Performance: No effects were observed with melatonin or temazepam on body temperature during early evening sleep, and there were no changes in performance after the sleep period with either drug.

In the present study on healthy volunteers using electroencephalography we have been unable to establish a consistent effect of melatonin on nocturnal sleep across the dose range 0.1 to 10.0 mg. The only change observed was that 5-mg led to a reduction in stage 3 in the first 100 min of sleep. A reduction in stage 3 and 4 sleep with 5 mg melatonin has been reported previously in studies on a simulated 9h phase advance [Stone et al., 1996], but it is considered that this minimal effect observed in the present study has little, if any, clinical significance. In contrast, the active control, temazepam (20 mg), had beneficial effects on various sleep parameters including reduced wakefulness and drowsy (stage 1) sleep and increased stage 2 sleep.

On the other hand, we were able to establish an unequivocal effect of melatonin on early evening sleep across the dose range 0.5 to 10.0 mg. The effect was fully developed with the 0.5 mg dose, with no additional effect observed above this dose. The increase in the number of REM periods observed during the early evening sleep was most likely due to an increase in total sleep time, as there was no change in the REM/non-REM ratio. Overall, the effect of melatonin was similar to that of 20 mg temazepam.

These studies suggest that melatonin is unlikely to possess useful hypnotic activity in healthy individuals when administered around the normal time of sleep, though the effect of melatonin on early evening, as opposed to nocturnal sleep, is comparable with that of a low dose of a benzodiazepine. Clearly, time of administration would appear to be a crucial factor in the appearance of the hypnotic activity of melatonin. In humans melatonin secretion occurs in the late evening [Tzischinsky et al., 1993], as was observed in the present experiment on nocturnal sleep. It is, therefore, possible that in healthy young adults the limited hypnotic activity of melatonin is fully developed with the normal nocturnal endogenous secretion and that raising the plasma level of melatonin, at that time, by ingesting melatonin, may have little, if any, further effect. On the other hand, daytime doses, which raise plasma melatonin levels to within or beyond the normal nocturnal range, improve sleep [Dollins et al., Nave et al., 1996, Reid et al., 1996, Hughes and Badia, 1997, Zhadanova et al., 1995, Nave et al., 1995]. This time-of-day dependent response, together with the absence of a dose response over the range 0.5 to 10.0 mg, suggests that the effect of melatonin is fully developed at the natural endogenous plasma level.

The hypnotic activity of melatonin observed after administration in the early evening was not accompanied by a chan1999]. In this way our results support the view of Nave et al [1995] and Tzischinsky and Lavie [1994] that the activity of melatonin is likely to be due to a direct effect on sleep rather than to any secondary effect of a fall in temperature. However, though other authors have reported changes in core temperature, [Reid et al., 1996, Hughes and Badia, 1997, Lushington et al., 1997, Gilbert et al., 1999], Nave et al [1998] have suggested that any hypothermic effect of melatonin occurs after the onset of hypnotic activity.

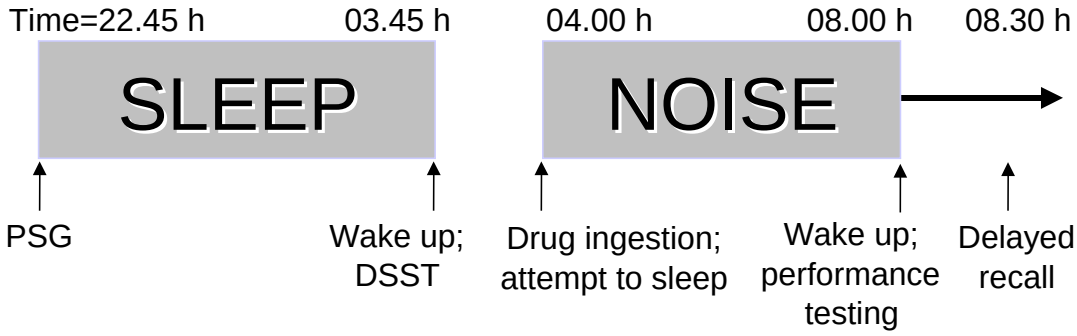
The present study has demonstrated that the hypnotic effect of melatonin is time-of-day dependent, and this, together with evidence that the ingestion of melatonin in certain circumstances may lead to sleep disruption [Middleton et al., 1996], suggests that melatonin is only likely to be useful as a hypnotic at certain times of the circadian cycle which have yet to be delineated. This raises the issue of a ‘window of effect’ but it is unlikely that any individual coping with sustained and continuous operations would possess sufficient information on their circadian rhythm of melatonin secretion to ensure ingestion of the compound at times to avoid sleep disruption and to ensure some beneficial effect on sleep. On the other hand, whether individuals coping with time zone changes can use melatonin for entrainment remains controversial, and the present study does not provide any input for the debate on the phase shifting properties of melatonin.

ZALEPLON

While benzodiazepines such as temazepam and related drugs such as zolpidem are suitable for use as sleep inducers in sustained and continuous operations, these drugs are only suitable if at least six hours intervenes between ingestion and the requirement to be alert. When shorter periods are available for sleep drugs such as temazepam are not suitable as their use would be associated with impaired performance. In addition there may be a requirement for middle of the night administration when sleep is disturbed by intrinsic or extrinsic factors.

For the treatment of middle of the night insomnia caused by an intrinsic condition in the individual or by environmental factors such as noise it is necessary to move to the most rapidly eliminated hypnotic recently introduced into clinical practice, zaleplon (Sonata‘®), a pyrazolopyrimidine compound that binds selectively to the γ-aminobutyric acid $(GABA)_A$ receptor complex [Beer et al. 1997.;Dämgen and Lüddens, 1999]. It is rapidly absorbed, with peak plasma concentrations at around 1h, and rapidly eliminated with a plasma elimination half-life of approximately 1h [Beer, Ieni AJR, Wu WH, *et al*, Hurst M and Noble S]. Zaleplon therefore has a rapid onset of action and a rapid elimination half-life and this profile is unlike any other hypnotic drug in the market today. The structure of zaleplon is unrelated to barbiturates, benzodiazepines and other hypnotic drugs. It also possesses agonist properties and it lacks many of the side effects commonly associated with other hypnotic drugs due to its short duration of action. It has been shown to have useful hypnotic effects in patients with insomnia [Dietrich and Farr 1995, Walsh et al 1998, 2000a, 2000b, 2000c, Ancoli-Israel et al 1999, Elie et al., 1999, Cluydts 2000, Drake et al 2000,], these effects included reduction in sleep onset latency and this was not associated with rebound insomnia on withdrawal or with any other withdrawal symptoms. In addition there was no tolerance during therapy reported. In this way zaleplon can be used as a treatment for those patients with sleep onset insomnia or indeed for those with situational insomnia which manifests itself with problems falling asleep. Thus zaleplon may prove to be an extremely useful drug in the treatment of insomnia associated with circadian rhythm disturbance such as jet lag or when required to work at night and sleep during the day. Its rapid onset and swift duration of action would suggest its use to aid sleep after eastward travel where it is necessary to fall asleep at a time when the circadian rhythm is at its alert phase. In those who are required to retire to bed earlier in order to anticipate an early start it may also help with problems falling asleep. However, many other short acting hypnotics may be useful in these circumstances although the lack of rebound insomnia with zaleplon may make it more suitable in those who carry out skilled work. The unique property of zaleplon is its ability to promote sleep in the middle of the night without any residual effects on performance on the following morning [Vermeeren et al 1998, Danjou et al 1999, Walsh et al 2000, Stone et al 2000, Volkerts et al 2000, Zammit 2000,]. The subjects were healthy volunteers with situational middle-of-the-night insomnia, rather than patients with sleep maintenance insomnia, as in the previous study, which can be inconsistent in an experimental context [Walsh JK et al, 2000] In a study carried out in the United Kingdom situational insomnia was induced using a sound stimulus, a method that has been used previously to investigate the hypnotic properties of benzodiazepines and the hormone melatonin [Saletu et al 1985, Saletu et al 1987, Waldhauser et al 1990, Gieschke et al 1994, Cluydts et al 1995, Terzano et al 1995, Parrino et al 1997]. Since the sound stimulus used in these previous studies (traffic noise or continuous white noise) disturbed sleep, but did not prolong sleep latency *per se*, a pure tone pulse, as this has been shown to increase sleep latency [Nakagawa 1987].

LPS and Performance in Noisy Environment



Noise = 80 db(A) 1 khz pure tone pulse of 50 sec duration with an intertone interval of 1 sec. Turned off after 10 min of persistent sleep or 2 h without sleep.

Zopiclone was used as an active control to indicate the sensitivity of the experimental procedures. It is an established hypnotic with an elimination half-life of around 5-h, and would be expected to have residual effects on performance 4 h after administration [Nicholson, 1998].

Thirteen healthy volunteers were studied. Before the study, an adaptation night in a single room was undertaken to familiarise each subject with the recording procedures and to establish whether their sleep patterns were normal. At least four days after the adaptation night, the subjects reported to the laboratory on two occasions separated by at least one night to establish whether they were sensitive to the sleep-disrupting effects of noise. On both of these occasions, after a 5 h sleep period (22:45-03:45) in a quiet environment, the subjects got up and completed a 4-min test of performance (the digit symbol substitution task). They returned to bed at 04:00 and, after ingestion of placebo (administered single blind), they were asked to fall asleep. On the first single-blind placebo night, there was no sound stimulus (the mean background noise level in the bedrooms was 36.8 dB [A], while on the second single-blind placebo night the subjects were exposed to a pure tone pulse described below). The sound stimulus was started at 04:00 and a recordist monitored the electroencephalogram and determined the latency to persistent sleep (10 min of stage 2, 3, 4, or rapid eye movement (REM) sleep, methods described below). The sound stimulus was stopped either after persistent sleep had been reached, or after 2 h if the subject did not fall asleep. At 08:00, 4 h after drug ingestion, the subjects were awoken, if necessary, and they completed a battery of performance tasks and assessments of well being (described below).

Only those subjects who had an increase of at least 10 min in the latency to persistent sleep (LPS) from the night without noise to the night with noise were included in the double-blind phase of the study. They subsequently reported to the laboratory on four occasions separated by a period of at least four nights. The experimental procedure was identical to the second single-blind placebo night, except that at 04:00, each subject was administered placebo, zaleplon 10 mg, zaleplon 20 mg, or zopiclone 7.5 mg, double-blind, on separate occasions according to a four-period randomised cross-over design.

Sound stimulus

The sound stimulus was an 80 dB[A] 1kHz pure tone pulse with an inter-tone interval of 1 s, rise-decay times of 2.5 ms, and a duration of 50 ms. The sound stimulus was recorded onto a computer and replayed simultaneously into each bedroom via loudspeakers positioned 1 m behind the subject's head. Before each test night, a sound level meter was positioned at the subject's pillow in each bedroom and used to ensure that intended noise levels were replayed and that noise doses did not exceed those permitted by UK Health and Safety legislation.

Psychomotor performance and memory tests

Subjects were trained to plateau performance on all tests before the study began and were observed during the tasks by means of closed circuit television. The tests were presented in the following order: digit symbol substitution, immediate word recall, critical flicker fusion, choice reaction time and delayed word recall.

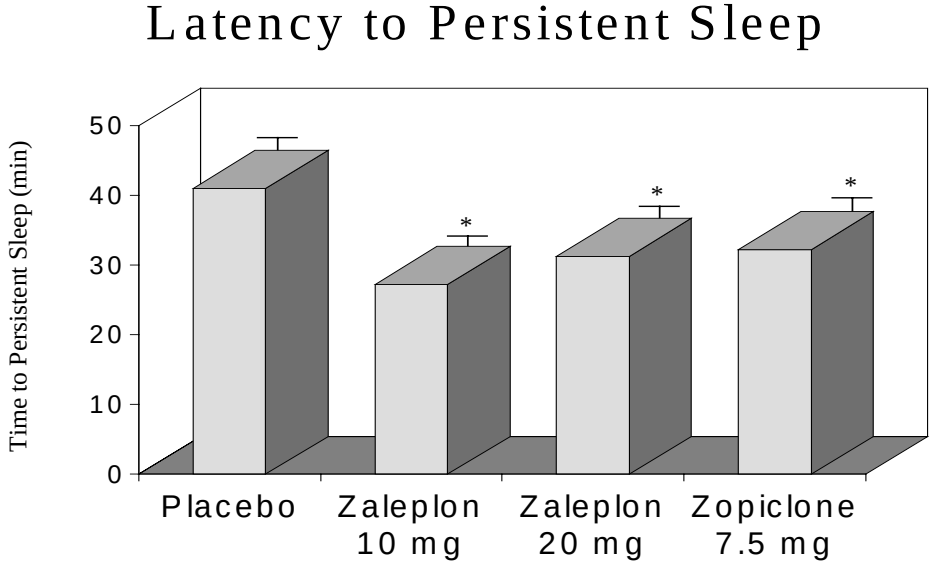
Electroencephalography

The subjects slept in single light-proofed, sound-attenuated, and air-conditioned rooms. Silver-silver chloride electrodes were used to record electroencephalograph (EEG) activity from the O_1-A_2 and C_4-A_1 positions, together with bilateral electro-oculograms (EOG) and the submental electromyogram (EMG), on a Nicolet Biomedical Ultrasom (digital EEG) system via three Nihon-Koden 4300 series EEG machines. A simulated paper speed of 10 mm/sec was used and each recording from the second period of sleep (04:00 to 08:00) was scored manually upon completion of the study into 30s epochs according to the criteria of Rechtschaffen and Kales [21]. Various measures were derived from the data for subsequent statistical analysis.

Statistical methods

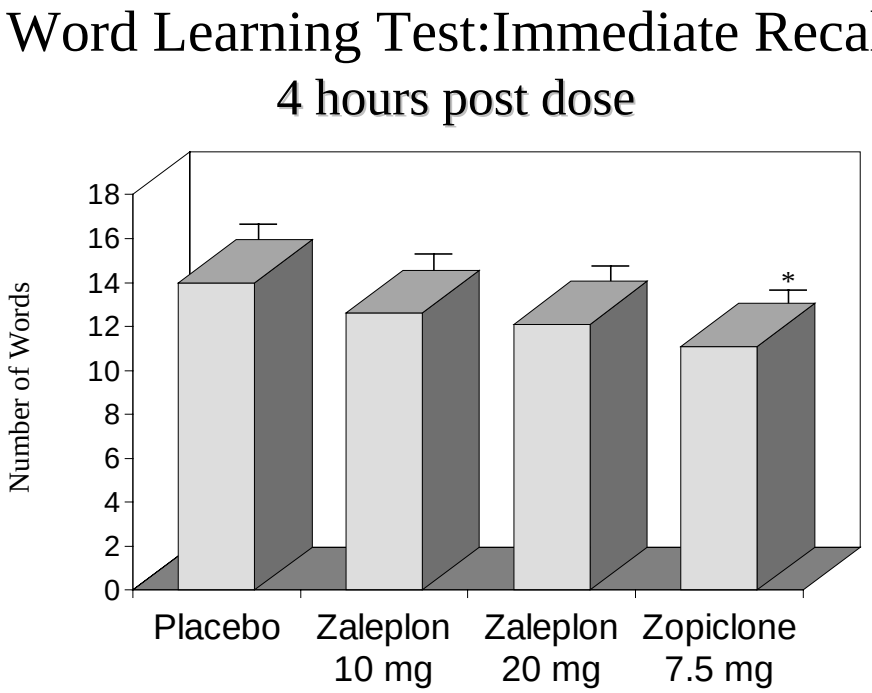
The sample size estimate was based on an estimate for the DSST of the standard deviation (6.78 symbols) of the difference between zaleplon 10 mg and placebo in a previous study [8]. The power calculation indicated that 12 subjects would be required to detect a difference of 6.1 symbols in the DSST with 80% power at the 5% significance level.

The data were analysed by an analysis of variance (ANOVA) with subjects, period, treatment, and first order carry-over as factors in the model. First order carry-over was not significant, and was therefore removed from the ANOVAs and least squares means calculated. A Bonferroni adjustment was made for the three active treatments compared with placebo. The 5%, 1% and 0.1% significance levels adjusted for multiple comparisons were: $p<0.0167$ (0.05/3); $p<0.0033$ (0.01/3); and $p <0.0003$ (0.001/3), respectively.



*$P<0.05$

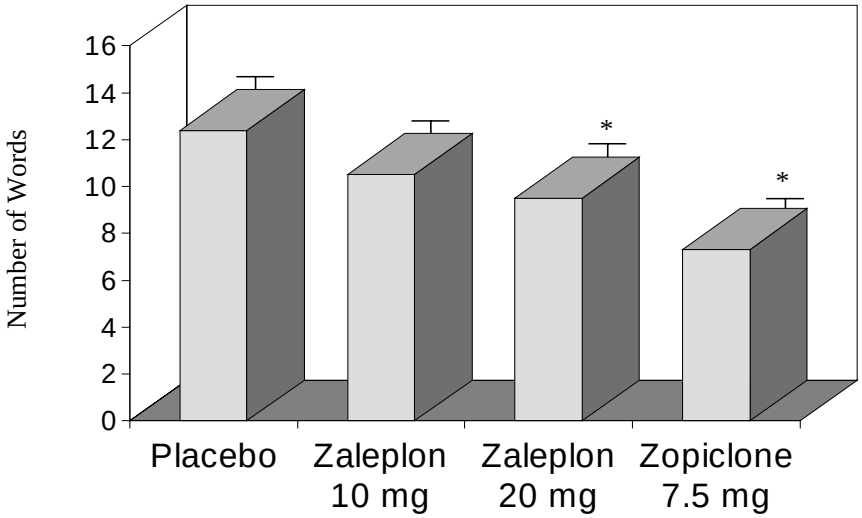
Figure 3



*$P<0.05$

Figure 4

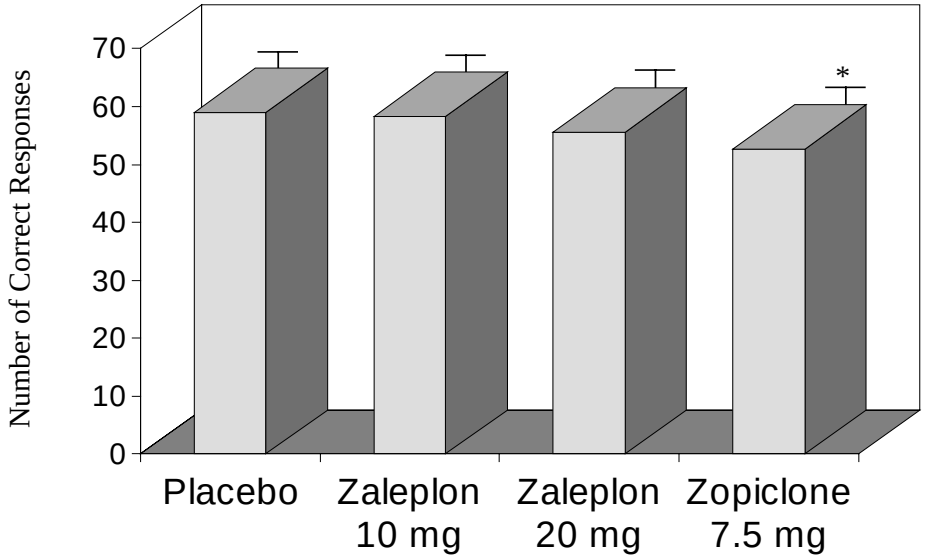
Word Learning Test:Delayed Word Recall
4.5 hours post dose



*P<0.05

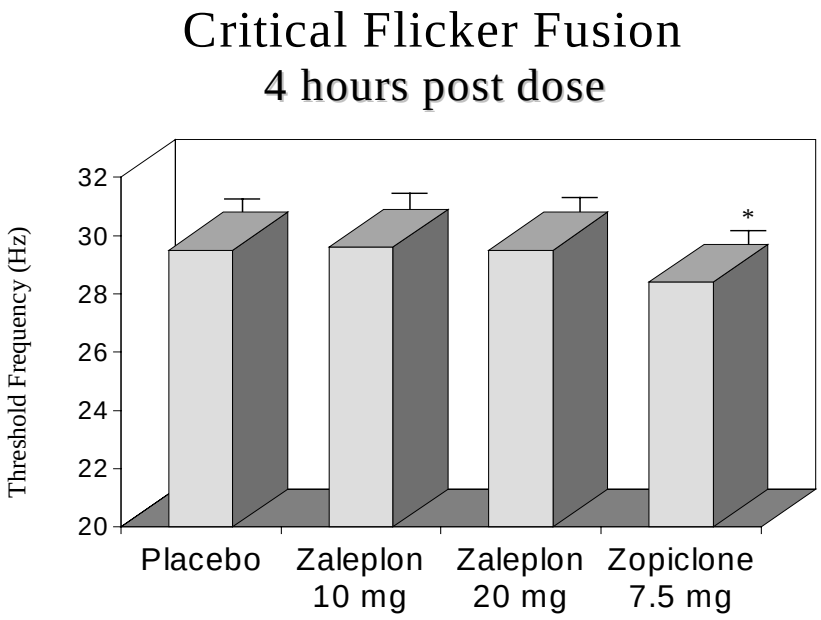
Figure 5

Digit Symbol Substitution Test
4 hours post dose



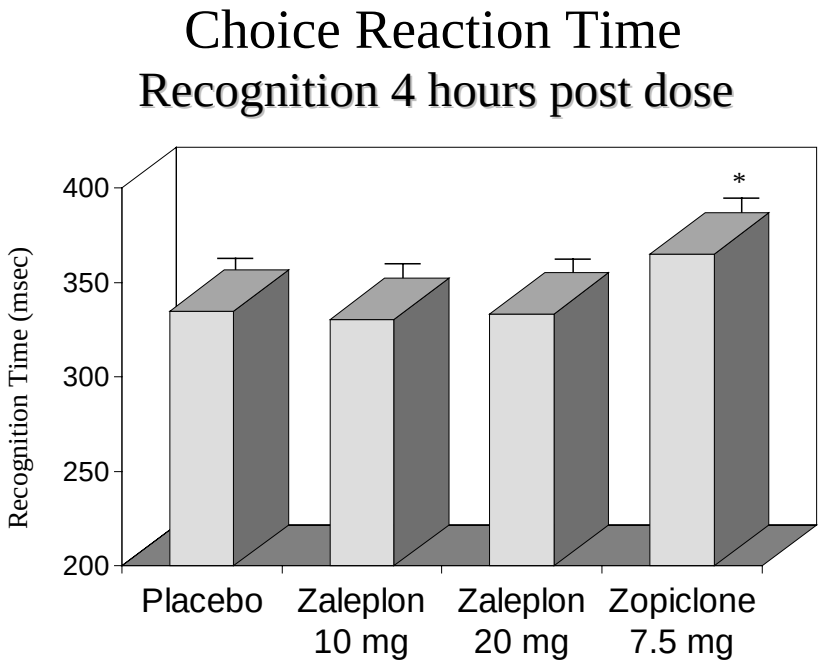
*P<0.05

Figure 6



*P<0.05

Figure 7



*P<0.05

Figure 8

Results

One subject was withdrawn from the study after the third drug treatment because drug treatments two and three had been administered in reverse order and therefore the order of treatment did not meet that specified by the randomisation.

No residual effects of zaleplon (10 and 20 mg) were found on psychomotor performance, memory, or subjectively assessed sedation. The active control, zopiclone (7.5 mg), impaired performance 4 h after ingestion on the digit symbol substitution task (p=0.004) and choice reaction time task (p=0.001), and reduced the number of words recalled on the delayed memory recall task (p=0.001), compared with placebo (Table I). However, the subjects as a group did not report any change in sedation 4-h after zopiclone ingestion, compared with placebo.

The latency to persistent sleep was reduced by both doses of zaleplon (10 mg, p=0.001; 20 mg, p=0.014) and the duration of stage 1 (drowsy) sleep was reduced by the 20 mg dose (p=0.012), compared with placebo (Table II). Zopiclone reduced stage 1 sleep (p=0.001), increased stage 3 sleep (p=0.0001) and increased total sleep time (p=0.003), compared with placebo.

No serious adverse events or discontinuations due to adverse events were reported during the study. The only treatment-emergent adverse event that was reported by more than one subject was a bitter after-taste with zopiclone (n=5 subjects, 38%).

Zaleplon appears to be a useful hypnotic for individuals who experience difficulty in falling asleep either at bedtime or in the middle of the night, as it is free from residual effects 4h after ingestion. Such sleep problems may be common as a sleep survey in the United States found that 56% of respondents reported difficulty in falling asleep and 67% reported awakening in the middle of the night [Ancoli-Israel and Roth, 1999)]. Many currently available hypnotics will sustain sleep and reduce the incidence of early morning awakenings if taken at bedtime. Given that the severity of an individual’s sleep problem is likely to vary from night to night, a potential benefit of zaleplon may be a reduction in the requirement for nightly prophylactic use of hypnotic medication. This may avoid the phenomenon of rebound insomnia after cessation of prolonged treatment. Clearly, assessment of the nature of the insomnia would be essential and patients would need to be given guidelines on the use of such a short-acting hypnotic in order to avoid ingestion of unnecessarily large prophylactic doses in an attempt to sustain sleep.

Little information is currently available on the effectiveness of zaleplon in healthy volunteers with transient insomnia. The present study suggests that the drug is likely to be useful following a westward time zone change when individuals may experience an early morning awakening and are unable to return to sleep. Zaleplon may also be effective if used occasionally to promote sleep in those who have to rest at unusual times of the day, for example, in the early evening before a night shift or for naps during military operations. However, further work would be required to establish whether zaleplon is useful in the management of this type of transient insomnia in healthy individuals involved in skilled activity when residual effects are to be avoided.

In conclusion, the present study has shown that zaleplon (10 mg and 20 mg) is free from residual effects 4h after ingestion in the middle of the night, and possesses hypnotic properties in a noise-induced sleep maintenance insomnia model in healthy subjects.

CONCLUSION

As far as sustained and continuous military operations are concerned the hypnotic temazepam remains the drug of choice for ensuring sleep during rest periods of six hours or more. Melatonin analogues may prove to be useful in the future Further studies on the use of zaleplon for short sleep periods during an irregular work/rest schedule are in progress.

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Comment réduire les effets du décalage horaire : les substances chronobiotiques (How to Alleviate Jet Lag/ The Chronobiotic Substances)

Médecin en Chef Didier Lagarde,* M.D., Ph.D. et
Médecin Principal Maurice Beaumont, M.D., Ph.D.**

* Délégation Générale pour l'Armement
DGA/DSP/STTC/SH
26 bd Victor
00457 Armées
France

** Institut de Médecine Aérospatiale
IMASSA
BP 73
91223 Bretigny/Orge
France

ABSTRACT: The current operational concept relies upon sustained or continuous operations that demand 24-hour round-the-clock capability so that they need a high level of performances overnight and a good quality of sleep during short rest periods before working. Otherwise, numerous missions need air transportation across multiple time zones, making the personnel exposed to jet-lag desynchronosis. This results in sleep disturbances, daytime sleepiness and performance impairment that tend to increase the hazard of mission failure and of casualties. Therefore, alleviating these disturbances appears to be of major interest. It can be proposed at first organisational methods consisting of adapting workload to individual's skill and of relieving personnel as much as possible, regarding mission's scheduling. Physiological methods are known to alleviate jet lag syndrome by taking naps of at least 30 min of duration at anytime in the nycthemeron and to hasten resynchronisation by exposure to bright light or darkness according to an appropriate schedule, by taking meals and practising physical exercises according to appropriate schedule. If all these methods cannot be applied due to environmental conditions, it can be proposed a pharmacological help using (i) hypnotic agents to promote sleep after the flight to assist in sleep timed to coincide with the nocturnal rest period at the destination or (ii) psychostimulant agents to maintain vigilance and performance during the flight and the following recovery period or (iii) melatonin to hasten the resynchronisation of the circadian system. We performed a real world study on jet lag called "operation Pegasus" that confirmed the hastening effect of melatonin on resynchronisation in a subjective rather than in an objective point of view but this study also brought some evidence of the positive effects of a new formulation of caffeine, slow release caffeine, in maintaining performance and vigilance during 10-12 hours following intake and also in speeding up the resynchronisation of biological rhythms. Therefore, we think that slow release caffeine could be included in a scheme of sleep/wakefulness management during continuous operations.

I- PREAMBULE

Le concept opérationnel actuel réside dans la réalisation d'opérations soutenues ou continues nécessitant un niveau de performances élevé et prolongé dès le déploiement de troupes. Nombreuses sont les missions qui s'effectuent Hors-Métropole, sous mandat des Nations Unies par exemple ; citons le déploiement d'une équipe médico-chirurgicale Française au Timor Oriental. Le transport des troupes peut alors inclure un vol transméridien de longue durée, c'est-à-dire un déplacement rapide avec franchissement de plusieurs fuseaux horaires. Communément appelé « jet-lag » par les auteurs anglo-saxons, les effets du décalage horaire lié à ce type de déplacement et la privation de sommeil fréquemment associés se traduisent par une fatigue, des troubles du sommeil, une somnolence diurne et une diminution des performances et de la vigilance qui peuvent nuire à la sécurité des personnels et/ou à la réussite de la mission (1).

Communication présentée lors du cycle de conférences RTO HFM sur « La gestion des rythmes veille/sommeil lors des opérations continues/soutenues », organisé à Fort Rucker, en Alabama aux Etats-Unis, les 17 et 18 juin 2002; à Varsovie, en Pologne, les 24 et 25 juin 2002; à Paris, en France, les 27 et 28 juin 2002, et éditée dans RTO-EN-016.

La gestion du rythme veille-sommeil en opération prend alors toute son importance, notamment lorsqu'il est impossible de relever assez fréquemment le personnel. Il peut être proposé des mesures organisationnelles ou ergonomiques portant sur l'adaptation de la charge de travail ou la rotation des personnels (2). Les méthodes physiologiques consistent à induire avant le départ une adaptation partielle au fuseau horaire du lieu d'arrivée (3) ou encore à inclure des petits sommes (« naps ») de façon éparse dans le nycthémère (2, 4). Les mesures pharmacologiques peuvent être appliquées soit pour induire le sommeil, soit pour prolonger l'état d'éveil ou encore pour faciliter la resynchronisation des rythmes biologiques.

L'une ou l'autre de ces mesures peut être appliquée pour atténuer le syndrome du décalage horaire, selon le profil type du vol et les conditions environnementales qui caractérisent le lieu d'arrivée. En outre, ces mesures seront plus ou moins efficaces en raison d'une variabilité individuelle extrême en regard de la sévérité du syndrome : un caractère extraverti, un tempérament "du soir" plutôt que "du matin", une grande motivation, un rythme de sommeil stable et un jeune âge sont en faveur d'un rétablissement rapide. De plus, le profil de sécrétion (amplitude et acrophase) de la mélatonine, hormone qui contrôle les rythmes de l'organisme comme nous le verrons, présente une grande variabilité interindividuelle mais une faible variabilité intra-individuelle d'une nuit à l'autre. Toutefois, un rythme biologique donné se resynchronisera d'autant plus rapidement que son amplitude est faible, ce qui est également soumis à une variabilité inter et intra individuelle. Il existe enfin une grande variabilité individuelle de la réponse au traitement pharmacologique du syndrome du décalage horaire, comme pour tout autre traitement.

Au cours de cet exposé, seront décrites les méthodes organisationnelles, physiologiques et pharmacologiques permettant d'atténuer le syndrome du décalage horaire. Avant de conclure, le descriptif de ces différentes méthodes sera suivi d'un exemple d'étude grandeur nature sur le décalage horaire dont la méthodologie et dont les principaux résultats seront présentés succinctement.

II- MESURES DE TYPE ORGANISATIONNELLE

Certaines mesures peuvent être prises avant le début du vol transméridien, d'autres pendant, mais aucune n'est efficace totalement en raison des variabilités individuelles exposées précédemment.

2.1- Les mesures à envisager avant le vol

Certaines sont faciles à appliquer et représentent un moyen important de la gestion de la vigilance.

2.1.1- L'information

Le personnel doit être informé de l'importance de la gestion de son sommeil avant le début de la mission

2.1.2- Le sommeil prophylactique

Un temps de sommeil de 4 heures le soir avant le vol de nuit peut conduire à une amélioration de la performance (5).

2.1.3- Le double équipage

Planifier le vol de longue durée en intégrant la possibilité de doubler l'équipage est une mesure évidemment très efficace bien que parfois difficile à appliquer.

2.1.4- La charge de travail et l'heure de début de la mission

Nicholson et son équipe (5) ont montré que le niveau de performance d'un équipage dépend de deux points essentiels : le rythme de travail sur plusieurs jours qui conditionne l'efficacité du sommeil et l'heure du début de la mission pour tenir compte de la rythmicité circadienne de la performance.

Il est ainsi conseillé :

- de limiter le nombre global d'heures de travail en fonction de la durée de la mission afin d'obtenir un sommeil réparateur au cours des périodes de repos. En raison d'un effet cumulatif des heures de travail irrégulier, le nombre global d'heures de travail compatible avec un sommeil efficace n'augmente pas linéairement avec le nombre de jours de mission. Par exemple, un équipage peut gérer 55 heures de travail sur une durée de 7 jours, mais seulement 25 heures de plus sur une durée de 14 jours. Il faut tenir compte de ce fait dans la programmation des missions sous peine d'un sommeil de mauvaise qualité et donc d'une diminution de la capacité opérationnelle.

- de déterminer l'heure du début de la mission en tenant compte de la rythmicité circadienne de la performance, dans le cadre d'une opération soutenue. En effet, la performance augmente de 5h00 à 17h00 et diminue de 17h00 à 5h00 chez les sujets synchronisés à l'alternance jour-nuit. Or, la durée du travail influe sur la performance : celle-ci est élevée au début de la mission, rejoint sa valeur habituelle à la 5ème heure de travail continu et se dégrade ensuite pour arriver à un palier minimal au bout de 12 heures. C'est pourquoi dans le cadre d'une opération soutenue, il vaut mieux commencer son service à 2h00 qu'à 14h00 : dans le 1er cas, le niveau de performance sera maintenu sur la durée de la mission car le niveau de performance élevé au début de la mission va compenser le creux circadien nocturne alors que la baisse de performance lors de la 2ème moitié de la période de travail va coïncider avec le niveau maximum diurne ; par contre, si le service commence à 14h00, la performance au cours de la 2ème moitié de la période de travail va être très dégradée puisque la baisse liée à la durée va coïncider avec le creux circadien nocturne.

2.1.5- Anticipation du décalage

Le processus adaptatif au décalage horaire peut être amorcé avant le départ, pour décaler progressivement le début et la fin des phases successives d'exposition quotidienne à la lumière et à l'obscurité et de la sorte avancer le pic de sécrétion de la mélatonine.

Par exemple, d'un point de vue pratique, les athlètes français participant aux jeux olympiques de Sydney avaient été soumis à un décalage horaire de 8 heures en avance de phase. Pour raccourcir activement la durée de la période de resynchronisation, la commission médicale du Comité National Olympique et Sportif Français leur avait proposé d'observer un calendrier précis dès le 5ème jour précédant le décollage. Il consistait à avancer d'une heure par jour, les horaires de lever et de coucher, de repas et d'entraînement physique. Dès le lever, il fallait s'exposer pendant 3 heures à un éclairage halogène intensif tout en réalisant un exercice physique, puis prendre une douche fraîche et un petit déjeuner. A l'inverse, en fin d'après-midi, il fallait ne plus s'entraîner, mais se relaxer, prendre une douche chaude et se coucher de plus en plus tôt.

Pendant le vol, il était recommandé de prendre des repas légers et de dormir pendant la seconde partie du trajet.

A l'arrivée, il était recommandé d'attendre la fin d'après-midi pour dormir, c'est-à-dire d'accumuler une dette de sommeil.

Pendant le séjour en Australie, le renforcement des synchroniseurs externes consistait à s'entraîner dès le matin et surtout entre 12h00 et 16h00, sous la lumière du soleil, sans porter de lunettes de soleil et à se relaxer le soir en ambiance calme et de faible luminosité ; une douche

chaude était préconisée pour faciliter l'endormissement, mais la prise de somnifères était proscrite.

2.2- Les mesures à envisager pendant l'opération

Le personnel doit aussi être informé de l'intérêt et de la nécessité de gérer son sommeil à l'arrivée pour limiter la privation de sommeil et la baisse de performance liées au décalage horaire. En effet, le meilleur remède contre une privation de sommeil est le sommeil lui-même. De courtes périodes de sommeil (siestes ou naps) d'une durée d'au moins une demi-heure, et même de 10 minutes ont montré leur efficacité sur le maintien d'une partie des performances (2, 4). Tout petit somme aussi court soit-il et quelle que soit sa place dans le nycthémére permettra de restaurer une partie des capacités du personnel mais il faut savoir que l'horaire de la sieste détermine son efficacité : les sommes les plus restaurateurs sont ceux qui sont pris entre 3h00 et 6h00 ou entre 16h00 et 18h00. De plus, les siestes sont suivies d'une période d'inertie de 15 minutes environ après le réveil, ce qui oblige à programmer ces périodes de sommeil en fonction des impératifs horaires de la mission.

III- MESURES PHYSIOLOGIQUES

Ces mesures physiologiques portent sur un renforcement des synchroniseurs externes des rythmes physiologiques et biologiques. Un rappel physiopathologique permettra de comprendre cette partie importante du traitement des troubles du décalage horaire.

3.1- Rappel sur la physiopathologie du décalage horaire

L'alternance jour-nuit est avec le rythme travail-repos, le principal synchroniseur externe chez l'homme. La lumière du jour synchronise l'horloge biologique interne, les noyaux suprachiasmatiques, grâce à des voies nerveuses issues de la rétine. Cette horloge est le véritable pacemaker des fonctions neurovégétatives. Celui-ci délivre, sans influence extérieure, de façon régulière et répétitive ses informations selon une périodicité de 25 h. Il reçoit aussi des informations provenant du monde extérieur et les transmet à une glande, l'épiphyse, qui sécrète une hormone, la mélatonine, pendant la nuit suivant l'alternance lumière/obscurité. La mélatonine dont la sécrétion est stimulée par l'obscurité et inhibée par la lumière diurne, permet l'ajustement de la période du noyau suprachiasmatique à 24 h : l'épiphyse est le resynchronisateur permanent de l'horloge principale. Les divers rythmes biologiques hormonaux (mélatonine, cortisol...), végétatifs (température, cycle veille-sommeil...) et comportementaux (activité, énergie...) auront ainsi une rythmicité circadienne renforcée. Le rôle de la mélatonine est donc de renseigner l'organisme sur la position de l'alternance jour/nuit, pour mettre en phase celui-ci avec son environnement.

Le décalage horaire induit un état de dyschronisme qui est la résultante de deux facteurs. D'une part, l'horloge biologique, réglée sur l'heure du pays d'embarquement, est décalée par rapport aux synchroniseurs externes (alternance lumière-obscurité, alternance travail-repos, horaires de prise des repas, etc.) auxquels elle est exposée dans le pays de destination : c'est la désynchronisation externe (6). D'autre part, les divers rythmes biologiques de l'organisme (sécrétions hormonales, température centrale, veille-sommeil) ne se resynchronisent pas à la même vitesse et vont ainsi se décaler entre eux : c'est la désynchronisation interne (7). La symptomatologie du décalage horaire apparaît après un vol de 5 fuseaux horaires ou plus et elle est d'autant plus marquée que le nombre de fuseaux horaires traversés augmente (8). Le sens du vol a son importance : un vol vers l'est, nécessitant une avance de phase (avancer l'heure de sa montre pour la faire coïncider avec l'heure solaire), est moins bien toléré qu'un vol vers l'ouest, nécessitant un retard de phase. Globalement, la capacité de resynchronisation des différents

rythmes biologiques de l'organisme sous l'action des synchroniseurs externes est estimée à 1 heure par jour pour un voyage vers l'est contre une 1h30 pour un voyage vers l'ouest.

3.2- Renforcement des synchroniseurs externes

Quoiqu'il en soit, ce délai de resynchronisation passive peut être raccourci par des mesures actives portant sur le renforcement des synchroniseurs externes à l'arrivée. Le plus puissant d'entre eux est l'alternance lumière obscurité.

3.2.1- La photothérapie

On peut utiliser un puissant éclairage halogène indirect d'au moins 10000 lux, mais la lumière du jour est encore plus efficace : ce processus d'éclairement est la photothérapie. Le contrôle horaire précis du début et de la fin de l'exposition à la lumière et à l'obscurité, selon les recommandations de Houpt et coll. (9), constitue ainsi un puissant moyen d'action sur le cycle veille-sommeil.

3.2.2- L'aspect nutritionnel

Ce contrôle du rythme jour-nuit doit être accompagné d'une hygiène de vie rigoureuse portant sur la quantité, la qualité et l'horaire de prise des repas. Le rôle des repas sur la performance (10), du glucose sur les processus de mémorisation (11) et de certains nutriments précurseurs de neurotransmetteurs, agissant sur les comportements (12) sont connus depuis des années. Les performances psychomotrices diminuent après un repas trop calorique (13) ou après un glucidique alors qu'un apport protéique serait moins pénalisant (14). Il apparaît que l'aliment glucidique à forte valeur hédonique, et de ce fait recherché quand la fatigue commence à faire son œuvre, risque de provoquer les quelques instants de somnolence en trop. La prise successive de petits repas comprenant des hydrates de carbone complexes et des aliments protido lipidiques permet d'assurer un apport calorique suffisant sans provoquer de pic insulino glucidique péjoratif au maintien de la vigilance. Par ailleurs, le fractionnement de la prise alimentaire permet de rompre la monotonie de ce type de situation.

3.2.3- La réduction du bruit

Le renforcement des synchroniseurs sociaux passe également par le contrôle de l'ambiance sonore grâce au port de bouchons d'oreille.

3.2.4- Exercice physique

La pratique d'un exercice physique sous la lumière du jour le matin permet d'accélérer la resynchronisation des rythmes circadiens (cf. §2.1.5).

3.3- Cas du séjour de courte durée

Un cas particulier est celui d'un vol transméridien vers l'est suivi d'un séjour très court, 48 heures au maximum, dans la zone d'arrivée et d'un retour dans la zone de départ. Dans ce cas, plutôt que d'essayer de se resynchroniser aux horaires du lieu d'arrivée sans en avoir le temps, mieux vaut essayer de conserver ceux de la zone de départ. Ceci impose dès l'arrivée, de se reposer la journée en ambiance calme (port de bouchons d'oreille), de faible luminosité (port d'un masque de sommeil) et de s'exposer la nuit à une lumière vive.

IV- MESURES DE TYPE PHARMACOLOGIQUE

Il est évident que certaines des recommandations de nature physiologique précédemment citées sont soit difficiles à suivre pour le militaire en opérations, soit inefficaces en raison du contexte. On peut alors proposer une aide pharmacologique pour faciliter la resynchronisation

des rythmes biologiques, pour induire le sommeil, ou encore pour maintenir et prolonger l'état d'éveil.

4.1- La mélatonine

La mélatonine est une hormone dérivée de la sérotonine, sécrétée par la glande pinéale (épiphyse) lors de l'obscurité (15). La sécrétion de mélatonine commence vers 21-22 h, atteint son pic vers 3 h (50-70 $pg.ml^{-1}$ dans le plasma), et cesse vers 7-9 h. Le profil de la mélatonine (amplitude et acrophase) présente une grande variabilité inter-individuelle mais une faible variabilité intra-individuelle d'une nuit à l'autre. Le rythme de la mélatonine est peu sensible aux effets de masquage (influence d'un stimulus externe) hormis celui engendré par la lumière. La demi-vie de la mélatonine administrée par voie orale est de 35 à 50 min ; son métabolite hépatique principal (90 %) est la 6-sulfomélatonine dont l'excrétion urinaire reflète bien la quantité de mélatonine sécrétée et permet une évaluation fiable et non invasive du rythme de la mélatonine.

Cette hormone reflète la longueur de la nuit et serait le messager de la photopériode, c'est-à-dire le signal temporel permettant de synchroniser les rythmes circadiens internes sur les synchroniseurs externes. Elle a un effet hypnogène rapide, transitoire et diminue l'état de vigilance et la température centrale pendant 3 à 4 heures, à la dose de 0.3 à 5 mg ; ces effets sont contraires à ceux induits par la lumière vive. L'apport de mélatonine exogène permet d'avancer ou de retarder les rythmes selon l'heure d'administration de l'hormone (16, 17). Ce pouvoir de la mélatonine exogène repose sur sa capacité à modifier la sécrétion endogène selon une courbe de réponse de phase et non par un phénomène classique de rétrocontrôle négatif. La courbe de réponse de phase de la mélatonine exogène est opposée à celle de la lumière : alors que le rythme de sécrétion de la mélatonine endogène et donc les rythmes circadiens sont retardés par une exposition à la lumière vive en début de nuit et avancés par une exposition en fin de nuit, la prise de mélatonine en début de nuit avance les rythmes mais elle les retarde quand elle est administrée en fin de nuit (18, 19). Les récepteurs de la mélatonine, présents dans le noyau suprachiasmatique et le cortex cérébelleux, ont une sensibilité maximale en fin d'exposition lumineuse (en fin de journée) et minimale en fin de sécrétion de mélatonine (au petit matin) ; c'est pourquoi il est plus facile d'obtenir une avance de phase par l'administration de mélatonine qu'un retard de phase, eu égard aux variations de sensibilité de ses récepteurs (20). De plus, les effets de la mélatonine exogène sur le système circadien sont moindres que ceux de la lumière : ainsi, la mélatonine exogène est incapable d'entraîner le rythme de la température interne (19).

Les études de toxicité chez le rat n'ont pas pu déterminer la dose létale 50. En l'absence de toxicité, l'administration de mélatonine exogène a été réalisée à plusieurs reprises chez l'homme dans le cadre d'études à des doses pharmacologiques pour mieux comprendre son rôle physiologique mais aussi envisager des applications thérapeutiques pour les troubles des rythmes biologiques. La mélatonine a montré un certain succès dans les cas d'insomnie par retard de phase, d'insomnie des personnes âgées, d'insomnie liée à la cécité et enfin d'insomnie liée au jet-lag. Mais ces études étaient basées essentiellement sur une évaluation subjective de l'effet de la mélatonine et rarement sur une évaluation objective.

En dehors de ces études, l'usage de la mélatonine est totalement libre et largement répandu aux Etats-Unis pour lutter contre les troubles du sommeil malgré l'absence d'une étude contrôlée prouvant indiscutablement son efficacité dans une indication précise. Le fait est que la Food and Drug Administration (FDA) classe la mélatonine non comme un médicament mais comme un supplément alimentaire ; aux Etats-Unis, l'hormone est préférentiellement extraite de la glande pinéale de bœuf. La mélatonine de synthèse est disponible sur prescription en Grande Bretagne et sa disponibilité est variable selon les pays. En France, elle n'a pas obtenu l'autorisation de mise sur le marché. Elle est en vente libre sur de nombreux réseaux Internet mais seules les fabrications sous licence garantissent l'origine synthétique, la pureté et le dosage de l'hormone.

De nombreuses études sur le terrain ont montré que l'administration de mélatonine exogène réduit les manifestations du décalage horaire, en particulier les troubles du sommeil et la somnolence diurne. La dose la plus couramment utilisée est de 5 mg mais le schéma d'administration est variable suivant les protocoles. La durée du traitement va de 3 à 9 jours ; il commence au plus tôt 3 jours avant le vol et au plus tard le lendemain du vol ; il finit en général 3 ou 4 jours après le vol, voire 5 ou 7. En fait une administration préventive trop précoce peut faire apparaître une somnolence par action sédative et hypnotique proprement dite de la mélatonine, mais aussi par son pouvoir de synchronisation. L'horaire de la prise du traitement doit être régulier : avant, pendant et après le voyage, elle doit correspondre à l'heure du coucher dans le pays d'arrivée. Pour un vol vers l'est, les prises préventives auront lieu en fin d'après-midi pour réaliser une présynchronisation, c'est-à-dire commencer l'avance de phase nécessaire à l'adaptation dans le pays de destination. Une fois arrivé, le traitement est pris au moment du coucher.

Au cours de ces études, on a donc pu démontrer une amélioration significative des symptômes du jet-lag par la mélatonine, mais il s'agissait presque toujours d'évaluations subjectives, au moyen d'échelles visuelles analogiques ou de questionnaires sur le sommeil, la vigilance, l'asthénie et l'humeur. L'unique évaluation objective du sommeil par actimétrie a montré une augmentation de la durée du sommeil (de 1 h environ) sous mélatonine (10 mg pendant 9 jours) mais aucun effet sur les performances, la vigilance et l'humeur (21). Par contre, l'évaluation objective de la resynchronisation des rythmes biologiques a montré une resynchronisation plus rapide des cycles de la mélatonine endogène et du cortisol (15, 22).

4.2- Les hypnotiques

De nombreuses études ont montré les effets des agents hypnotiques sur les perturbations du sommeil liées au décalage horaire (23-25). Les benzodiazépines constituent la plus grande classe de la famille des hypnotiques ; elles sont connues pour faciliter l'endormissement, réduire la fragmentation du sommeil et augmenter la durée totale de sommeil chez le sujet sain et l'insomniaque. Le zolpidem et la zopiclone qui ne sont pas des benzodiazépines ont de plus tendance à augmenter la durée de sommeil lent profond. Un élément déterminant de l'utilité de ces substances est leur durée d'action (23). Ainsi, les bénéfices attendus de l'usage de ces médicaments peuvent être masqués par des effets indésirables qui diminueraient la capacité opérationnelle après la période de repos. Après un vol transméridien, les agents hypnotiques dont la durée d'efficacité est comprise entre 3 et 5 heures peuvent être prescrits pour maintenir le sommeil pendant la phase d'adaptation aux nouveaux horaires, sans aucun effet délétère sur la performance. Dans de telles situations, les hypnotiques agissent plus probablement par leur effet inducteur de sommeil que par un hypothétique effet resynchronisant (26).

Les hypnotiques ont donc un intérêt évident dans le cadre du décalage horaire ; ils en ont également un dans celui des opérations continues. Ainsi, le témazépam, une benzodiazépine dont la demi-vie est comprise entre 5 et 8 heures, a été utilisé pour induire le sommeil de récupération des pilotes anglais impliqués dans la guerre des Malouines en 1982 (27). La durée d'incapacitation étant de 6 heures au maximum, il importait de coordonner la prise de la substance avec le planning de la mission.

4.3- Les psychostimulants

Un niveau d'éveil compatible avec la réalisation de missions nocturnes peut être maintenu avec des substances psychostimulantes. Les amphétamines, utilisées depuis des décennies, ont de graves effets secondaires cardio-vasculaires (tachycardie), végétatifs (hyperthermie, risque de coup de chaleur) et neurologiques (altération du sommeil de récupération, tolérance, syndrome de sevrage) (28) qui limitent leur emploi dans le temps. D'autres molécules éveillantes ont montré leur capacité à maintenir les performances

psychomotrices et cognitives pendant 12 heures (pémoline) à 48 voire 64 heures (modafinil), tout en étant dépourvues d'effets secondaires majeurs (4, 29-32). Enfin, de nombreuses recherches portent sur les possibilités d'utilisation de la caféine en conditions opérationnelles (33). Parce que l'effet éveillant du café est fugace (34) et que ses effets secondaires (tachycardie, tremblements, irritabilité, diurèse) ne sont pas négligeables (28), une nouvelle forme galénique de caféine, la caféine à libération prolongée (LP), a été récemment mise au point par le centre de recherches de la société Nestlé (Nestec, Vevey, Suisse). La caféine LP apporte une cinétique adaptée à un véritable traitement car elle permet un effet pharmacodynamique optimal pendant l'éveil tout en assurant des taux plasmatiques de caféine trop faibles au coucher pour interférer avec l'endormissement (atteinte du plateau plasmatique dans les quatre heures suivant la prise et maintien de ce plateau pendant 4 à 6 heures) (35). De plus, les concentrations obtenues 24 heures après l'administration sont insuffisantes pour permettre, sur une courte période d'administrations répétées, une accumulation de caféine susceptible d'engendrer des effets adverses. Lagarde et coll. (36) ont montré les effets de trois doses différentes (150, 300 et 600 mg) de caféine LP chez le sujet humain privé de sommeil pendant 32 heures et ont observé le meilleur rapport efficacité/effets indésirables avec la dose de 300 mg. La même équipe a montré que la caféine LP à cette dose de 300 mg est aussi efficace que le modafinil (200 mg) pour maintenir la vigilance et les performances cognitives au cours d'une privation partielle de sommeil de 18 heures en horaires décalés (15h00-9h00) (37).

La caféine à libération prolongée, par son effet psychostimulant, constitue ainsi un traitement symptomatique de la somnolence observée au décours du décalage horaire. Elle pourrait également en être un traitement étiologique car elle facilite la resynchronisation des rythmes biologiques après une privation de sommeil (38). Ceci pourrait s'expliquer par une limitation de la sécrétion endogène de mélatonine par un effet antagoniste de la caféine s'exerçant sur les récepteurs A_{2b} à l'adénosine présents notamment sur les cellules de la glande pinéale.

Les propriétés psychostimulantes et resynchronisantes de la caféine à libération prolongée laissent à penser qu'elle pourrait être efficace pour atténuer le syndrome du décalage horaire. De plus, l'efficacité de la mélatonine sur ce syndrome n'a été vérifiée que d'un point de vue subjectif. Nous avons donc réalisé une étude de terrain (Opération Pégase) pour, d'un point de vue objectif, confirmer l'efficacité de la mélatonine et pour évaluer l'intérêt de la caféine à libération prolongée dans l'atténuation du syndrome de jet-lag.

V- OPERATION PEGASE

Cette étude a été effectuée en coopération avec l'Armée de l'Air Française, l'US Air Force et l'US Air Force Research Laboratory de Brooks, Texas, pour montrer l'intérêt d'une aide pharmacologique dans le maintien de l'efficacité opérationnelle d'une troupe après un décalage horaire Ouest-Est de 7 heures.

Les effets de la mélatonine exogène (5 mg) et de la caféine LP (300 mg) sur la resynchronisation des principaux rythmes biologiques ont été comparés de façon subjective mais aussi objective versus placebo, selon un protocole randomisé, contrôlé et en double aveugle.

27 volontaires (18 hommes, 9 femmes, 15 Caucasiens, 9 Hispaniques et 3 Afro-Américains, âge: 35.3 ± 8.1 ans.; poids: 77.6 ± 15.8 kg; taille: 170 ± 10 cm) issus d'une unité de Réserve de l'US Air Force ont participé à cette étude, dont le protocole expérimental avait été agréé par les comités d'éthique de l'hôpital Robert Ballanger d'Aulnay sous Bois, France et de l'hôpital de San Antonio, Texas, Etats-Unis.

Ces volontaires sont restés 6 jours et nuits à Brooks Air Force Base, les 5 premiers ont été consacrés à la synchronisation des rythmes circadiens et aux procédures de familiarisation aux différents tests, les $6^{èmes}$ jour et nuit ont été consacrés à l'enregistrement des variables de référence. Le lendemain, les sujets sont partis pour Mont de Marsan, France, par un vol de 9

heures vers l'est à travers 7 fuseaux horaires. La période de resynchronisation des rythmes prise en compte dans l'étude s'est étendue sur les 10 jours et 9 nuits qui ont suivi l'arrivée puis les sujets sont repartis aux Etats-Unis.

Les sujets ont été séparés en 3 groupes homogènes de 9 personnes : un groupe a reçu une gélule de caféine LP (300 mg) à 7h00 locales pendant les 5 premiers jours de la période de resynchronisation ; un autre groupe a reçu une gélule de mélatonine (5 mg) la veille du vol à 17h00 locales, le jour du vol à 16h00 locales et les 3 premiers jours en France à 23h00 locales, selon le protocole préconisé par Arendt et coll. (15, 39) ; le 3ème groupe a reçu une gélule de placebo aux mêmes horaires que les deux autres groupes.

140 paramètres ont été pris en compte pour évaluer le sommeil, les performances cognitive, psychomotrice et physique, l'humeur, l'état clinique et hormonal. Plus précisément, le sommeil a été mesuré par enregistrement électroencéphalographique (EEG) selon des critères standard (40) et par des agendas de sommeil (41), les performances cognitive et psychomotrice par des tests de la STRES Battery de l'OTAN (36), la performance physique par la mesure de la force des poignets et de la puissance musculaire des membres inférieurs (42), la somnolence diurne par des tests subjectifs et par actimétrie (43-45), la fatigue centrale par un test CFF (critical flicker-fusion test) (46, 47) et l'humeur par des échelles visuelles analogiques (48). De plus, les déphasages et la resynchronisation des rythmes circadiens ont été évalués par des mesures de la température centrale et des dosages salivaires de la mélatonine et du cortisol, ces 3 paramètres sont en effet des marqueurs reconnus du système circadien (49). Sauf pour ce qui concerne les enregistrements EEG du sommeil et l'enregistrement actimétrique en continu, tous les tests ont été effectués la veille du vol (référence) et chaque jour de la période de resynchronisation le matin entre 9h00 et 12h00 et l'après-midi entre 14h00 et 17h00, ces horaires correspondant respectivement aux périodes d'hypervigilance et d'hypovigilance de l'individu (50).

Les principaux résultats ont confirmé l'effet délétère du décalage horaire sur le sommeil qui était perturbé durant les 5 premières nuits, si bien que les sujets étaient somnolents pendant les 5 premiers jours de la période de resynchronisation ; les performances étaient également amoindries.

La mélatonine n'a pas modifié le sommeil ni amélioré la vigilance qui sont restés comparables à ceux du groupe placebo. Si la performance physique du groupe mélatonine est maintenue (force de la main), voire augmentée (force des membres inférieurs) pendant les premiers jours de resynchronisation, il n'en est pas de même avec la capacité attentionnelle qui est diminuée le 1er jour ni avec les performances cognitives (STRES Battery) dont 2 paramètres seulement ont été améliorés en 5 jours. Aucune étude portant sur l'évaluation objective des performances cognitives sous mélatonine n'avait été réalisée jusqu'ici. La mélatonine améliore principalement l'humeur et la qualité subjective du sommeil, mais diminue aussi la sensation de fatigue liée au décalage horaire (15). L'augmentation des performances physiques pourrait justement être liée à l'amélioration de l'humeur et à une plus grande motivation des sujets.

Les sujets du groupe caféine ont vu une nette amélioration de leurs performances cognitives et physiques dans les 5 jours suivant le vol. Le test CFF est nettement amélioré dans les heures qui ont suivi la 1ère prise du traitement (J1 au matin) et aussi l'après-midi, ce qui s'explique par l'atteinte du plateau plasmatique de caféine LP en 4 heures et par son maintien pendant 6 heures (35). La caféine LP a amélioré 24 paramètres évalués par la Stres Battery portant notamment sur le temps de réponse et le nombre de bonnes réponses aux divers tests de raisonnement et de mémorisation, la capacité attentionnelle (effet non significatif), ainsi que la force de la main et l'endurance des muscles des membres inférieurs. Il est intéressant de noter que la caféine LP n'a amélioré que les paramètres dégradés par le décalage horaire, et non pas les performances qui n'étaient pas préalablement affectées (51). Nous avons retrouvé dès le 2ème jour de la resynchronisation, l'effet éveillant bien connu de la caféine. Cet effet sur la vigilance s'est rapidement estompé à partir du 5ème jour correspondant à l'arrêt de la prise de caféine, ce

qui confirme les résultats d'une autre étude qui a montré que la durée d'efficacité de la caféine LP ne dépasse pas 9 à 13 heures suivant la prise (36). Ces améliorations des niveaux de performance et de vigilance ont été observés sans aucun effet indésirable de la caféine LP sur le sommeil.

Enfin, cette étude a confirmé la désynchronisation du système circadien sous l'effet du décalage horaire chez le groupe placebo et l'effet resynchronisant de la mélatonine dès le 6ème jour suivant le vol transméridien. Il est très intéressant de noter que les rythmes du cortisol et de la mélatonine du groupe caféine LP étaient resynchronisées également au 6ème jour, ce qui laisse à penser que la caféine LP pourrait aussi exercer une action chronobiotique.

VI- CONCLUSION

En raison d'une dégradation des niveaux de performances et de vigilance, le syndrome du décalage horaire constitue un problème majeur aussi bien en milieu militaire en raison de l'augmentation importante du nombre de missions dans des zones éloignées en latitude qu'en milieu civil en raison de l'explosion du nombre de passagers transportés.

L'intensité et la fréquence de ce syndrome en dépit de variations inter individuelles importantes justifient la mise en place de mesures plus ou moins efficaces et pratiques selon le contexte environnemental.

Les mesures organisationnelles à type d'adaptation de la charge de travail et de recherche de la plus grande adéquation possible entre les compétences individuelles et le poste de travail sont loin d'être à négliger.

L'amélioration des niveaux de vigilance et de performances doit être recherchée dans un premier temps par des mesures physiologiques consistant à dormir par périodes courtes, dès qu'on le peut, en tenant compte du planning de la mission et à observer une hygiène de vie (exercice musculaire, repas, exposition à la lumière) rigoureuse.

Lorsque ces mesures sont difficilement applicables, une aide pharmacologique légère caractérisée par son efficacité, son innocuité et sa facilité d'administration doit être prise en considération. Les hypnotiques de nouvelle génération pris après le vol aident à caler le sommeil sur les horaires du lieu d'arrivée, et les psychostimulants comme le modafinil maintiennent la vigilance et les performances pendant 48 heures sans effet secondaire majeur et la mélatonine accélère la resynchronisation des rythmes biologiques.

L'étude « opération Pégase » a confirmé l'effet resynchronisant de la mélatonine sur le plan subjectif ; le fait marquant de ce travail est l'intérêt que peut apporter la caféine à libération prolongée dans la gestion de la veille et des performances en opération incluant un décalage horaire. En effet, cette substance exerce un effet psychostimulant classique mais de longue durée (10-12 heures), associé à des propriétés resynchronisantes des rythmes biologiques : par la conjugaison de ces deux actions, la caféine LP atténue de façon importante le syndrome du décalage horaire.

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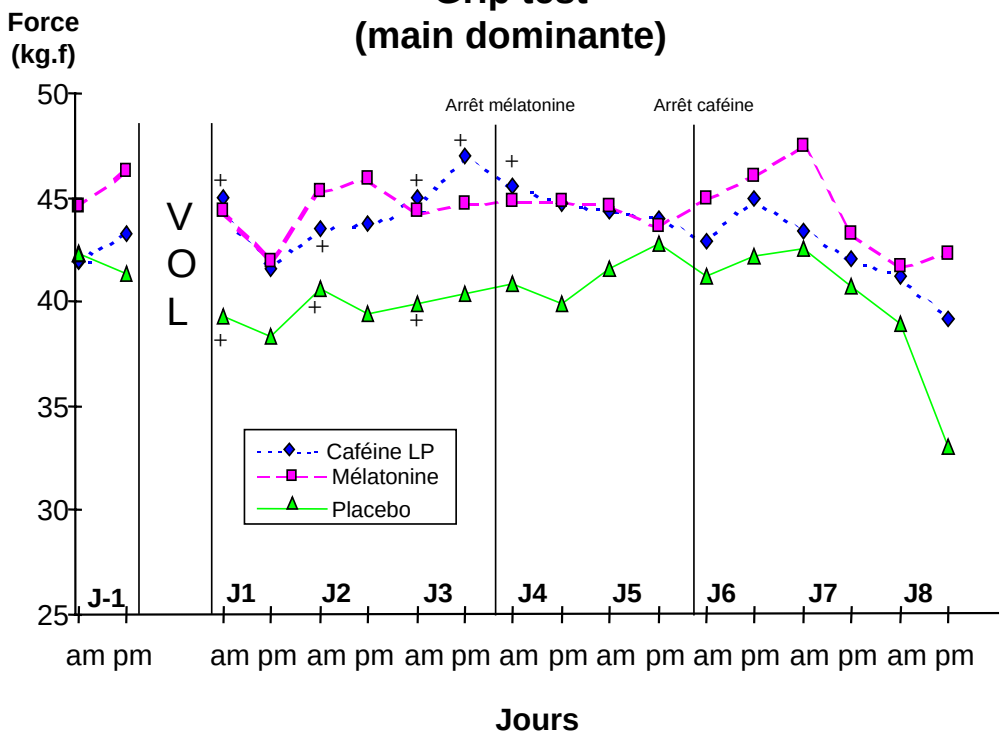
S.T.R.E.S. Battery

Opération PEGASE

Grip Test

Opération PEGASE



JUMP TEST

Opération PEGASE

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ABSTRACT

Food, Exercise and Ergonomic Measures

Maria Casagrande
Dipartimento di Psicologia – Università degli Studi di Roma "La Sapienza"
Aeronautica Militare Italiana, CSV, Reparto Medicina Aerospaziale
Pratica di Mare, Pomezia (Roma)

Arousal levels during wakefulness are neither stable nor homogeneous but vary in a periodical or near periodical manner, with a main decrease in night-time hours and in the early afternoon hours. In protracted waking conditions, there is an increase in sleepiness in the circadian phases destined for sleep. It must, however, be remembered that sleep is not only governed by circadian factors (process C), responsible for sleep relegation in particular moments of the day, according to the environmental light-dark cycle, but also by homeostatic ones (process S) which express sleep need with a pressure that grows monotonically during wakefulness and also decreases in the same constant manner during sleep. Sleepiness also increases as a result of protracted wakefulness and reaches a peak in conditions of extreme pressure in both processes (S and C) which regulate sleep. Sleepiness and vigilance have a chronobiological organisation with a bimodal distribution. As regards sleepiness, there is a main night-time peak and a secondary afternoon one that has a lower intensity and extent. The chronobiological organisation of vigilance has a daytime peak between 10.00 and 11.00 a.m. and an evening peak between 9.00 and 11.00 p.m. The two trends co-vary such that an earlier afternoon peak in sleepiness will match an earlier evening peak in vigilance. A circadian modulation is also found in performance which fluctuates according to the type of performance concerned. Finally, chronobiological variations are even found as regards physical exercise and food that in turn can modulate vigilance levels. Physical exercise can alter the individual circadian rhythm and seems to have a positive role in quickly adapting to changes in the sleep-wake cycle. Food can also affect vigilance levels with effects that depend on the amount and type of food eaten as well as on when it is eaten. In general, carbohydrate-rich foods (pulses, pasta, potatoes) tend to increase sleepiness and to promote sleep while high protein foods (meat, eggs) promote vigilance. As regards dietary effects on vigilance, we should also not overlook the widespread use of caffeine (coffee, tea, chocolate, Coca Cola). There are many scientific works which confirm the objective efficacy of this substance in improving certain kinds of psychomotor performance, above all when protracted wakefulness does not exceed 36 hours. It must, however, be recalled that indiscriminate use (i.e. before experiencing feelings of fatigue or sleepiness) of caffeine substances may quickly lead to developing a tolerance to these stimulants with the resulting progressive loss of efficacy. Indeed, too much caffeine (>600 mg/day) may lead to so-called "caffeinism", characterised by anxiety and disturbed sleep, and may even have harmful effects.

Paper presented at the RTO HFM Lecture Series on "Sleep/Wakefulness Management in Continuous/ Sustained Operations", held in Fort Rucker, Alabama, United States, 17-18 June 2002; Warsaw, Poland, 24-25 June 2002; Paris, France, 27-28 June 2002, and published in RTO-EN-016.

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REPORT DOCUMENTATION PAGE

1. Recipient's Reference	2. Originator's References	3. Further Reference	4. Security Classification of Document
	RTO-EN-016 AC/323(HFM-064)TP/39	ISBN 92-837-1073-8	UNCLASSIFIED/ UNLIMITED

5. Originator

Research and Technology Organisation
North Atlantic Treaty Organisation
BP 25, F-92201 Neuilly-sur-Seine Cedex, France

6. Title

Sleep/Wakefulness Management in Continuous/Sustained Operations

7. Presented at/sponsored by

the Human Factors and Medicine Panel (HFM) and the Consultant and Exchange Programme of RTO presented on 17-18 June 2002 in Fort Rucker, Alabama, United States, on 24-25 June 2002 in Warsaw, Poland, and on 27-28 June 2002 in Paris, France.

8. Author(s)/Editor(s)	9. Date
Multiple	November 2002
10. Author's/Editor's Address	**11. Pages**
Multiple	146

12. Distribution Statement

13. Keywords/Descriptors

Sleep deprivation
Stress (physiology)
Fatigue (biology)
Drugs
Amphetamines
Physiological effects
Human factors engineering
Military operations
Pharmacology
Continuous operations (CONOPS)
Caffeine
Work/Rest cycles
Stress management
Hypnotics and sedatives
Sleep
Pharmacology
Modafinil
Sustained operations (SUSOPS)
Stimulants
Circadian rhythms
Jet lag
Sleep loss
Sleep management
Sleep Wakefulness rhythm

14. Abstract

To preserve a good level of vigilance and performance, we have to respect our sleep-wakefulness cycle. The sustained and continuous operations induce disturbances of this biological rhythm, such as sleep loss, jet-lag.... There is an antinomy between the physiological requirement and the operational requirement. To be able to continue the mission but also to preserve our security and the security of the crew we need an appropriate sleep-wakefulness management. This Lecture Series presents the physiological, ergonomic and pharmacological possibilities to reach these goals.

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Printed by St. Joseph Print Group Inc.
(A St. Joseph Corporation Company)
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ISBN 92-837-1073-8