

UNCLASSIFIED

**Defense Technical Information Center
Compilation Part Notice**

ADP013763

TITLE: An Overview of Sleep Deprivation and The Ameliorative Effects of Modafinil

DISTRIBUTION: Approved for public release, distribution unlimited

This paper is part of the following report:

TITLE: Sleep/Wakefulness Management in Continuous/Sustained Operations

To order the complete compilation report, use: ADA412900

The component part is provided here to allow users access to individually authored sections of proceedings, annals, symposia, etc. However, the component should be considered within the context of the overall compilation report and not as a stand-alone technical report.

The following component part numbers comprise the compilation report:

ADP013762 thru ADP013770

UNCLASSIFIED

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 as 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.

...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 consequences¹.

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.

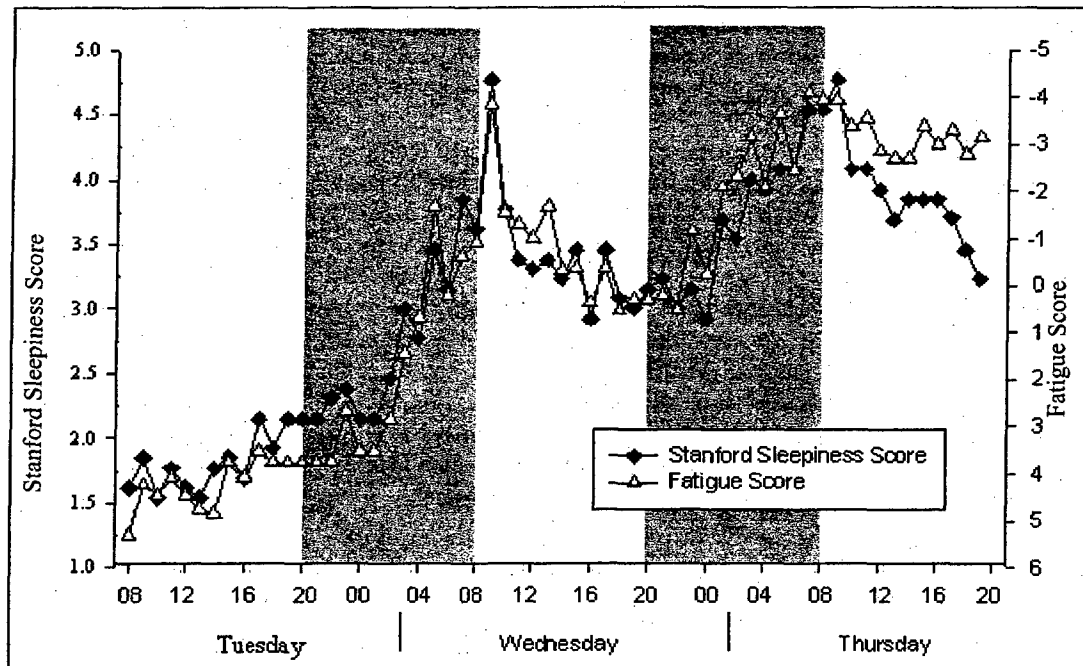


Figure 1: SAM Fatigue and Stanford Sleepiness Scales

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' than 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'.

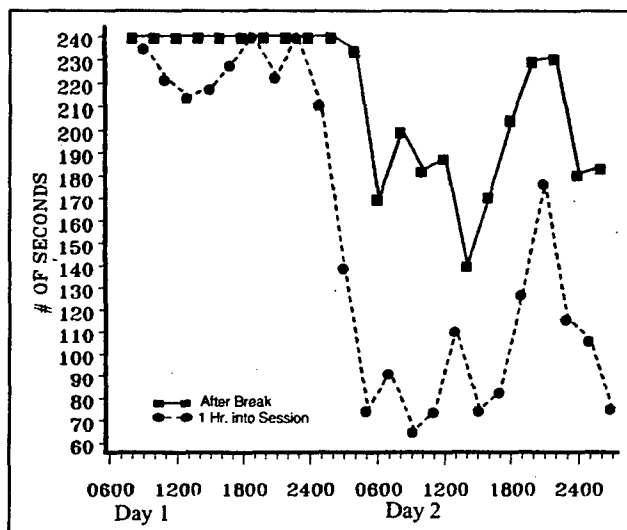


Figure 2A: Sleep onset latencies during the 4 minutes eyes closed task.

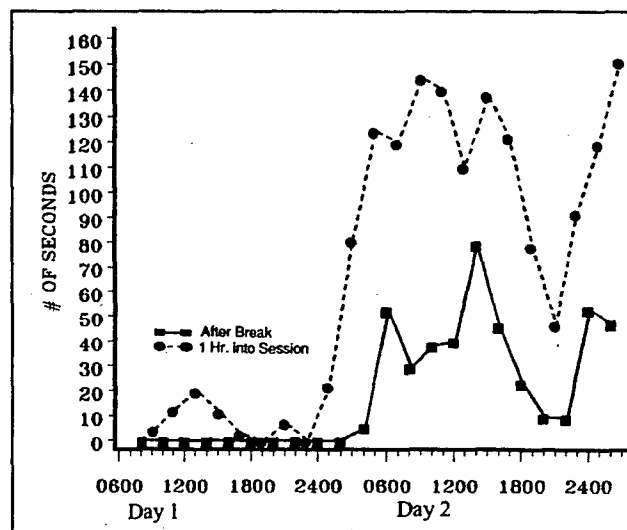


Figure 2B: Total sleep time during the 4 minutes eyes closed task.

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.

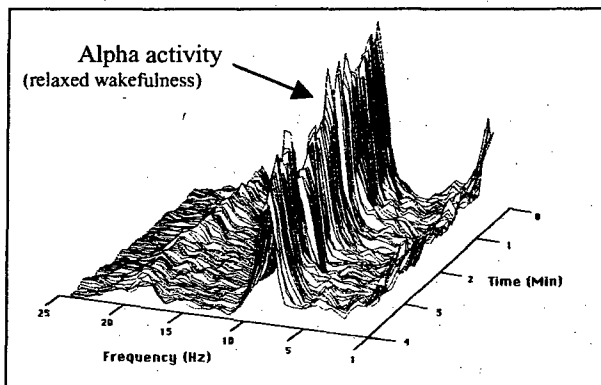


Figure 3A: 5 Hrs Awake

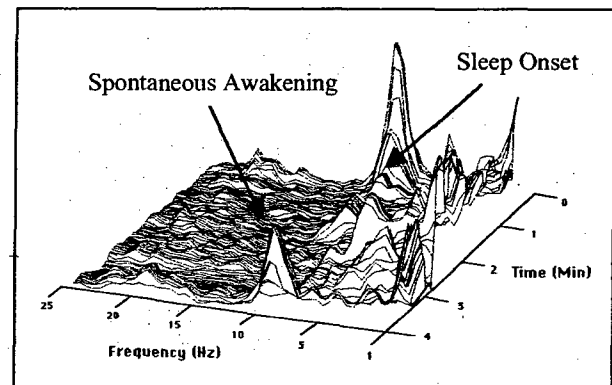


Figure 3B: 25 Hrs Awake

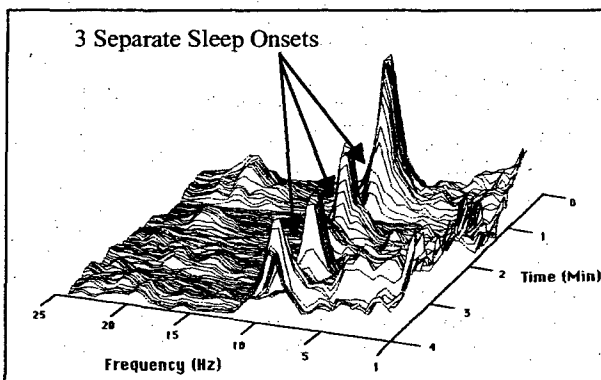


Figure 3C: 31 Hrs Awake

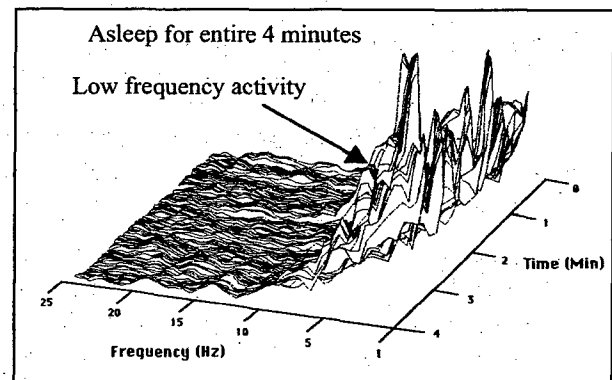


Figure 3D: 45 Hrs Awake

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 derive the EEG index was: $\left(\frac{A}{A_b}\right) - \left(\frac{T + D}{T_b + D_b}\right) + 1$ where A, T and D refer to Alpha, Theta and Delta activity generated during the 4 min sessions, and A_b , T_b and D_b 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.

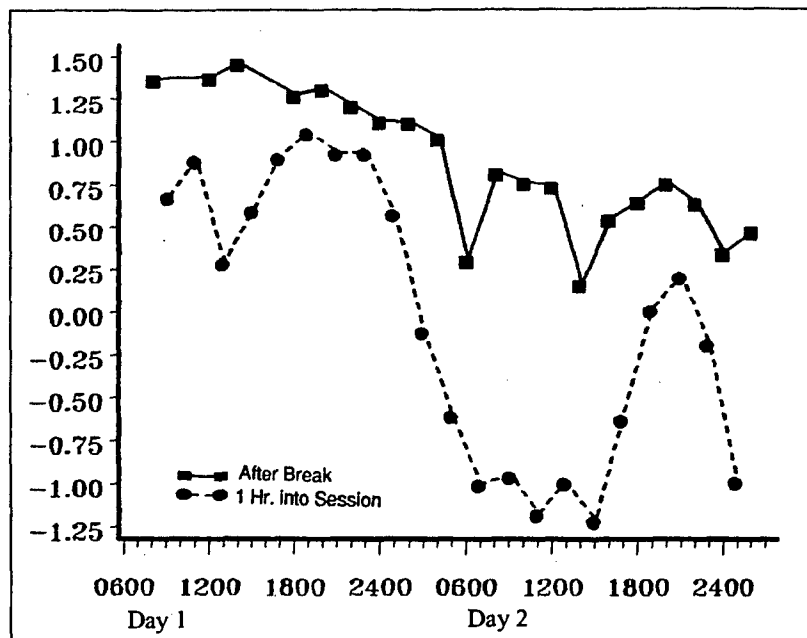


Figure 4: EEG Drowsiness Index

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.

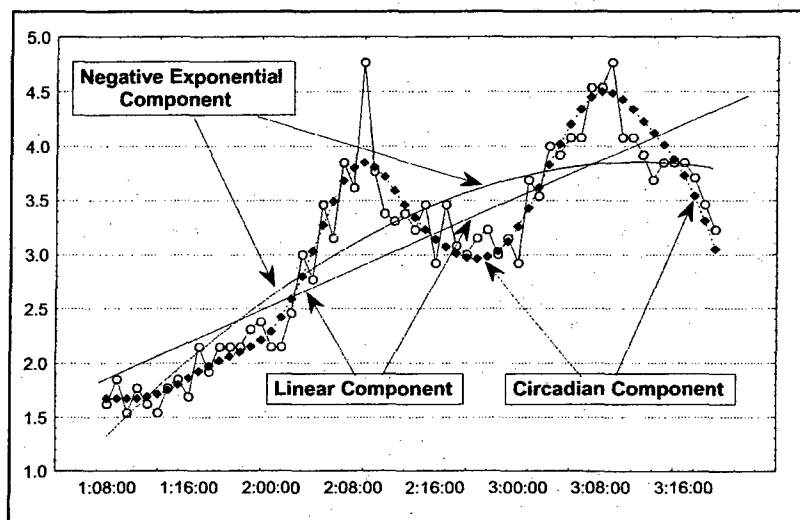


Figure 5: Results of Complex Demodulation on Stanford Sleepiness Scores

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.

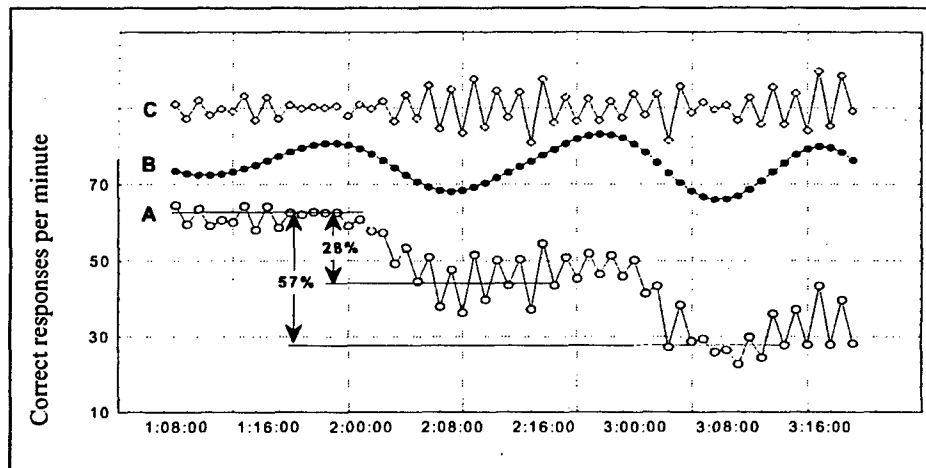


Figure 6 : Serial Reaction Time

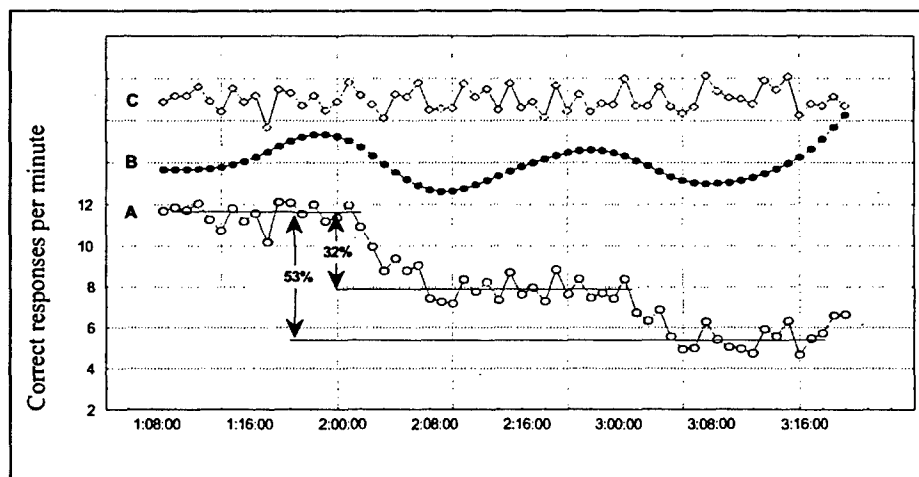


Figure 7: Logical Reasoning Task

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 wakefulness². 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).

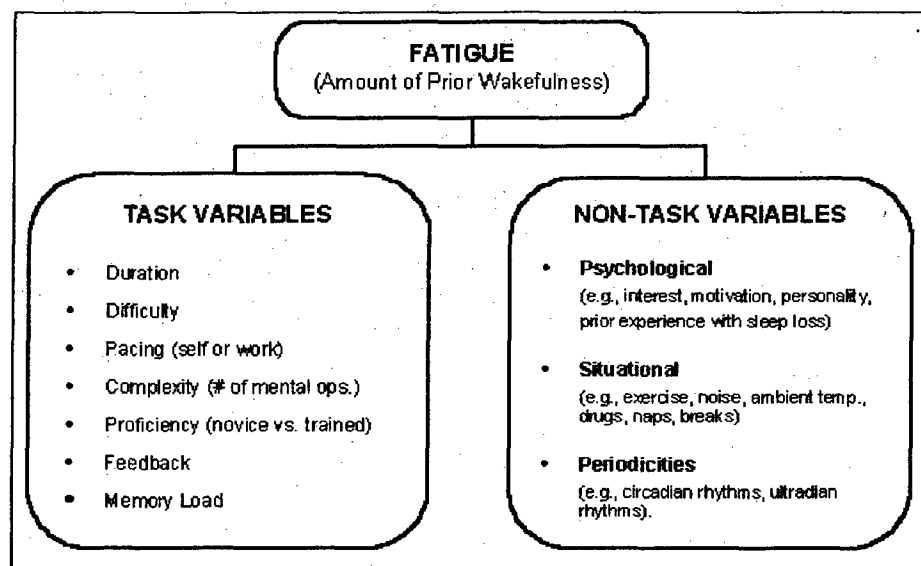


Figure 8: Johnson's (1982) 3 classes of modifying variables

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
<i>Duration</i>	Long	Short
<i>Difficulty</i>	Hard	Easy
<i>Pacing</i>	Work-paced	Self-paced
<i>Complexity</i>	Low	High
<i>Proficiency</i>	Novice	Expert
<i>Feedback</i>	No	Yes
<i>Memory Load</i>	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 subclass 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).

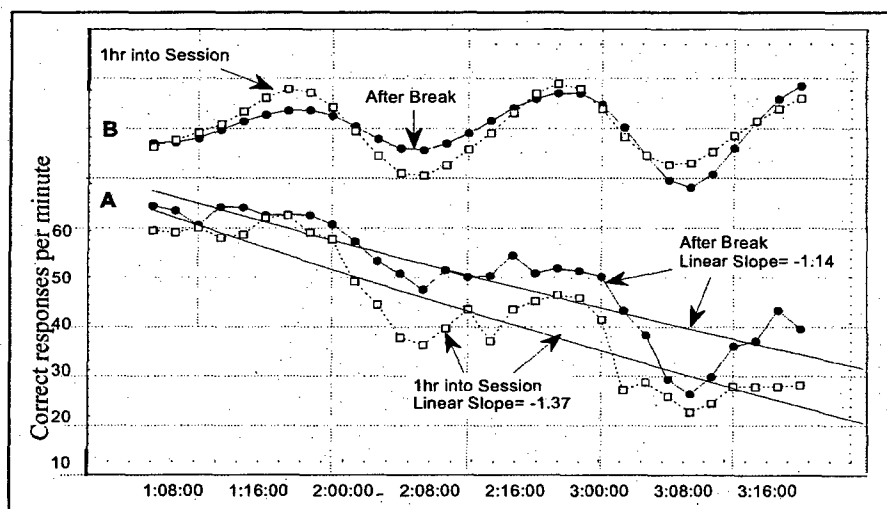


Figure 9: Serial Reaction Time

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 can 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.

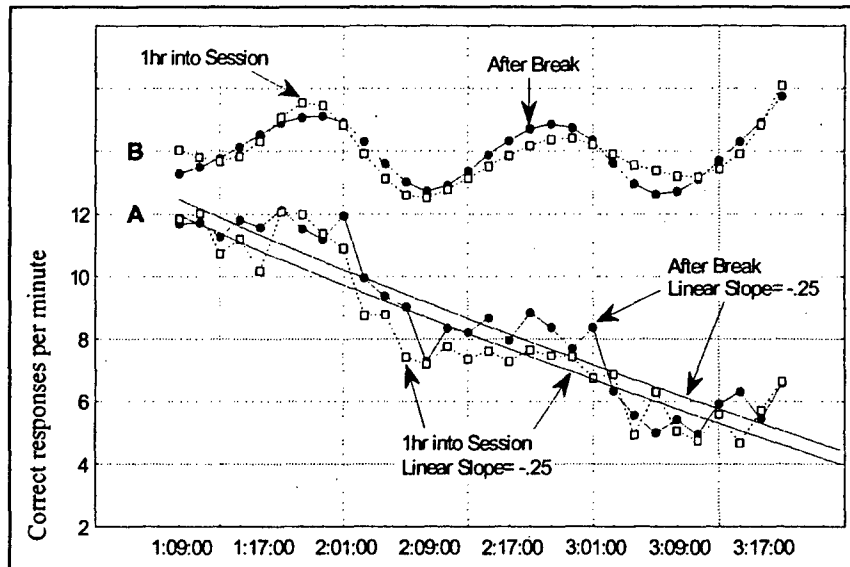


Figure 10: Logical Reasoning Task

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 interactions it should not be surprising that sleep deprivation has proven to be a complex field of study.

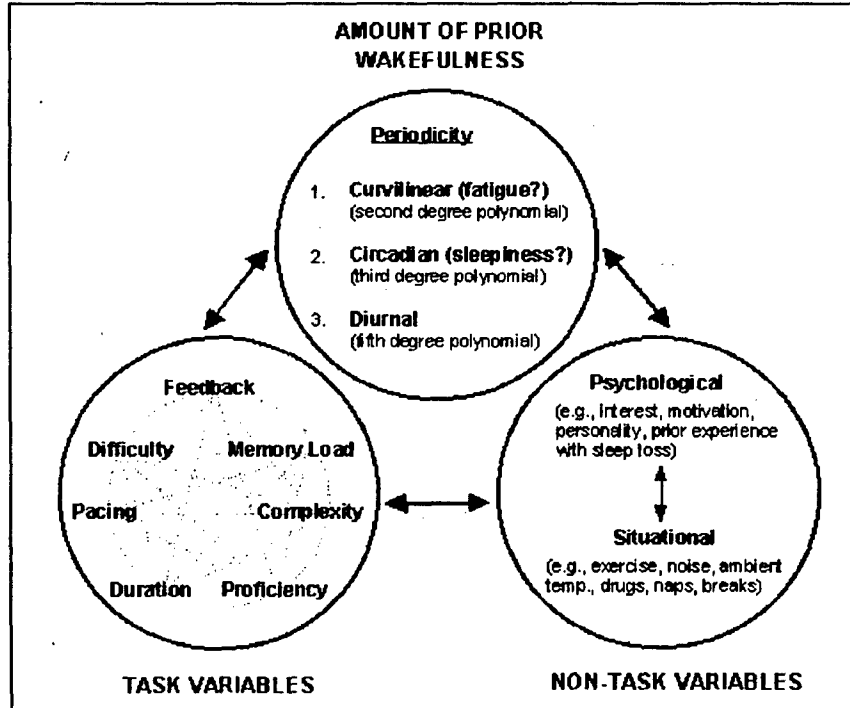


Figure 11: Effects due to sleep deprivation

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 05:30⁴.

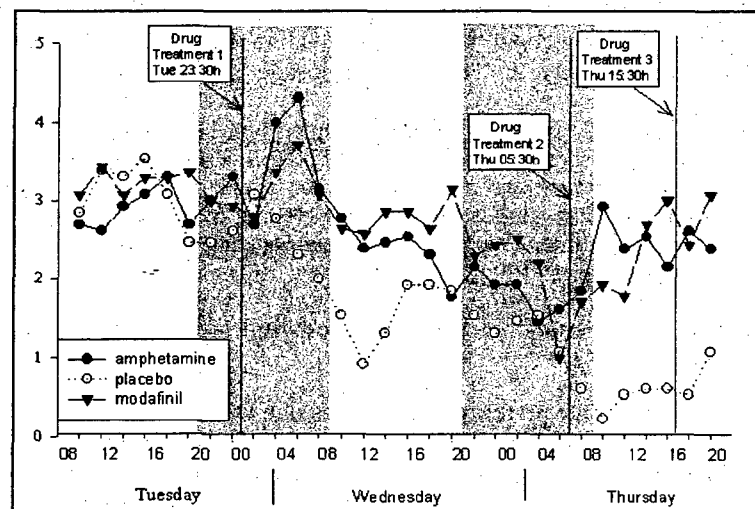


Figure 12: I Feel Alert

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.

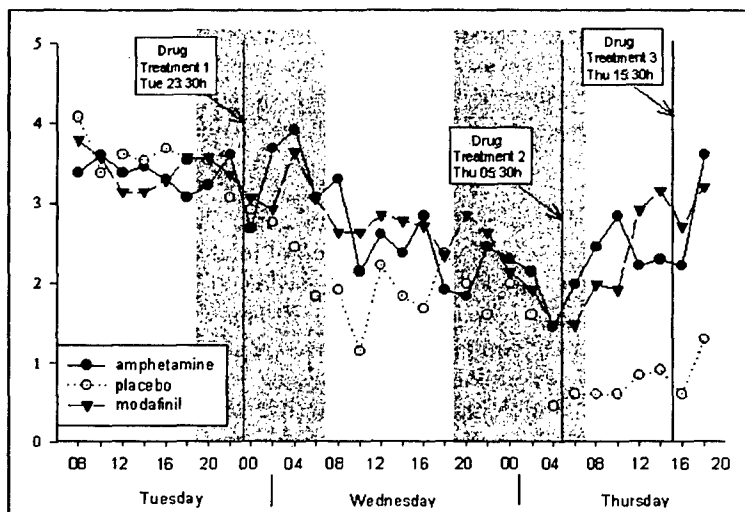


Figure 13: I Feel Good

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 I.

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.

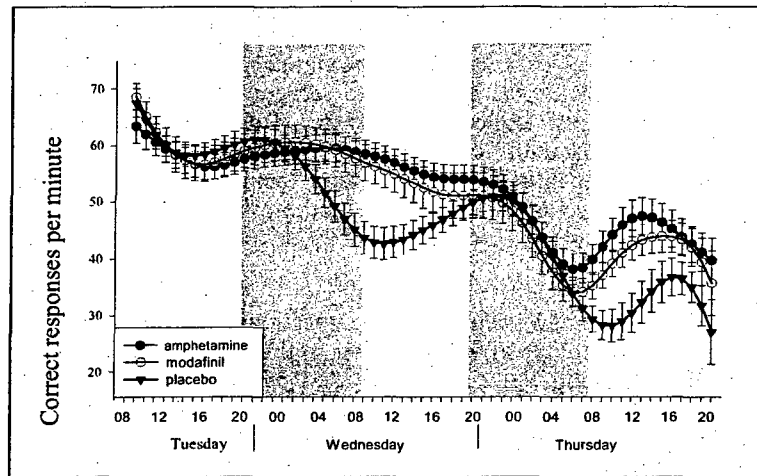


Figure 14: Linear and circadian trend data for the Serial Reaction Task

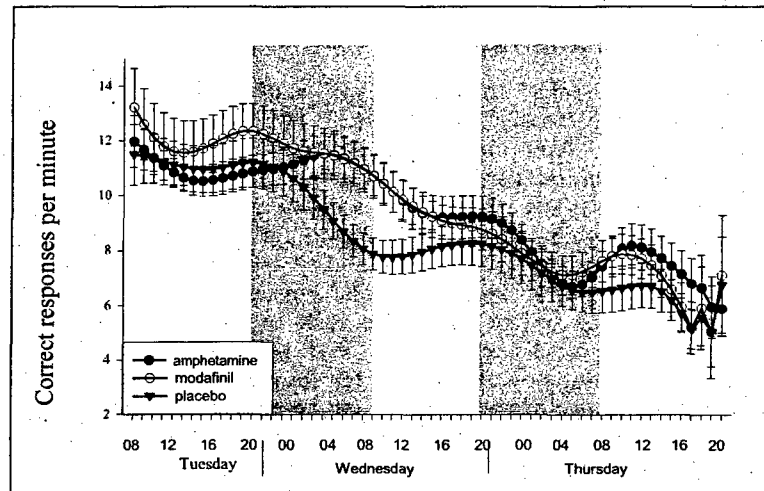


Figure 15: Linear and circadian trend data for the Logical Reasoning Task

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 underestimated (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 its 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.

Bibliography

1. Angus, R.G., Heslegrave, R.J., and Myles, W.S., Effects of prolonged sleep deprivation, with and without chronic physical exercise, on mood and performance. *Psychophysiology*, 1985. 22, p. 276-282.
2. Angus, R.G., Pigeau, R.A., and Heslegrave, R.J., Sustained-operations studies: From the field to the laboratory, in *Why We Nap: Evolution, Chronobiology, and Functions of Polyphasic and Ultrashort Sleep*, C. Stampi, Editor. 1992, Birkhauser: Boston. p. 217-241.
3. Babkoff, H., Caspy, T., Mikulincer, M., and Sing, H., Monotonic and rhythmic influences: A challenge for sleep deprivation research. *Psychological Bulletin*, 1991. 109(3), p. 411-428.
4. Baranski, J.V., Pigeau, R.A., and Angus, R.G., On the ability to self-monitor cognitive performance during sleep deprivation: A calibration study. *Journal of Sleep Research*, 1994. 3, p. 36-44.
5. Baranski, J.V., and Pigeau, R.A., Self-monitoring cognitive performance during sleep deprivation: Effects of modafinil, d-amphetamine and placebo. *Journal of Sleep Research*, 1997. 6, p. 84-91.
6. Baranski, J.V., Cian, C., Esquivié, D., Pigeau, R.A., and Raphel, C., Modafinil during 64 Hr of sleep deprivation: Dose-related effects of fatigue, alertness, and cognitive performance. *Military Psychology*, 1998. 10(3), p. 173-193.
7. Baranski, J.V., Gil, V., McLellan, T.M., Moroz, D., Buguet, A., and Radomski, M., Effects of modafinil on cognitive performance during 40 hours of sleep deprivation in a warm environment. (manuscript submitted for publication), 2001.
8. Bastuji, H., and Jouvet, M., Successful treatment of idiopathic hypersomnia and narcolepsy with modafinil. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 1988. 12, p. 695-700.
9. Batéjat, D.M., and Lagarde, D.P., Naps and modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. *Aviation, Space and Environmental Medicine*, 1999. 70(5), p. 493-498.
10. Benington, J.H., Sleep homeostasis and the function of sleep. *Sleep*, 2000. 23(7), p. 959-966.
11. Bensimon, G., Benoit, O., Lacomblez, L., Weiler, E., Warot, D., Weil, J.S., and Puech, A.J., Antagonism by modafinil of sleep-deprivation induced psychomotor and cognitive impairment in 12 healthy volunteers. *Psychiatrie and Psychobiologie*, 1989. 4(4), p. 193-254.

12. Besset, A., Tafti, M., Villemin, E., and Billiard, M., Effects of modafinil 300 mg on sleep, sleepiness and alerting of narcoleptic subjects. *Journal of Sleep Research*, 1992. 1, p. 23.
13. Billiard, M., Picard, E., Besset, A., and Maurel, A. Treatment of narcolepsy-cataplexy with modafinil, an Alpha 1 adrenoceptor agonist. in *5th European Congress of Sleep Research*. 1987.
14. Billiard, M., Laffont, F., Goldenberg, F., Weill, J.S., and Lubin, S., Placebo-controlled, crossover study of modafinil therapeutic effect in narcolepsy. *Sleep Research*, 1991. 20, p. 289.
15. Billiard, M., Besset, A., Montplaisir, J., Laffont, F., Goldenberg, F., Weill, J.S., and Lubin, S., Modafinil: A double-blind multicentric study. *Sleep*, 1994. 17, p. S107-S112.
16. Bjerner, B., Alpha depression and lowered pulse rate during delayed actions in a serial reaction test: A study in sleep deprivation. *Acta Physiologica Scandinavica*, 1949. 19(Suppl. 65).
17. Boivin, D.B., Montplaisir, J., Petit, D., Lambert, C., and Lubin, S., Effects of modafinil on symptomatology of human narcolepsy. *Clinical Pharmacology*, 1993. 16, p. 46-53.
18. Borbely, A.A., A two-process model of sleep regulation. *Human Neurobiology*, 1982. 1(3), p. 195-204.
19. Borbely, A.A., Achermann, P., Trachsel, L., and Tobler, I., Sleep initiation and initial sleep intensity: interactions of homeostatic and circadian mechanisms. *Journal of Biological Rhythms*, 1989. 4(2), p. 149-160.
20. Borbely, A.A., and Achermann, P., Concepts and models of sleep regulation: an overview. *Journal of Sleep Research*, 1992. 1, p. 63-79.
21. Bourdon, L., Jacobs, I., Bateman, W.A., and Vallerand, A.L., Effect of modafinil on heat production and regulation of body temperatures in cold-exposed humans. *Aviation, Space and Environmental Medicine*, 1994. 65, p. 999-1004.
22. Brun, J., Chamba, G., Khalfallah, Y., Girard, P., Boissy, I., Bastuji, H., Sassolas, G., and Claustrat, B., Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during 36h sleep deprivation. *Journal of Sleep Research*, 1998. 4, p. 229-241.
23. Buguet, A., Montmayeur, A., Pigeau, R., and Naitoh, P., Recovery sleep after 64 hours of continuous cognitive work: double-blind comparison of modafinil vs. placebo and d-amphetamine in 40 young adults. *Journal of Sleep Research*, 1995.
24. Cajochen, C., Brunner, D.P., Graw, P., and Wirz-Justice, A., Power density in Theta/Alpha frequencies of the waking EEG progressively increases during sustained wakefulness. *Sleep*, 1995. 18(10), p. 890-894.
25. Caldwell, J.A., Caldwell, J.L., Smythe, N.K., and Hall, K.K., A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: A helicopter simulator study. *Psychopharmacology*, 2000. 150(3), p. 272-282.
26. Caldwell, J.L., and Caldwell, J.A., Recovery sleep and performance following sleep deprivation with dextroamphetamine. *Journal of Sleep Research*, 1997. 6, p. 92-101.
27. Carskadon, M.A., and Dement, W.C., Sleep tendency: an objective measure of sleep loss. *Sleep Research*, 1977. 6, p. 200.
28. Carskadon, M.A., and Dement, W.C., Effects of total sleep loss on sleep tendency. *Perceptual & Motor Skills*, 1979. 48, p. 495-506.
29. Carskadon, M.A., and Dement, W.C., The Multiple Sleep Latency Test: What does it measure? *Sleep*, 1982. 5(2), p. S67-S72.
30. Cohen, M.S., Freeman, J.T., and Wolf, S., Metarecognition in time-stressed decision making: Recognizing, critiquing, and correcting. *Human Factors*, 1996. 38(2), p. 206-219.
31. Coren, S., *Sleep Thieves: An Eye-Opening Exploration into the Science & Mysteries of Sleep*. 1996, New York, NY: The Free Press.

32. Corsi-Cabrera, M., Arce, C., Ramos, J., Lorenzo, I., and Guevara, M.A., Time course of reaction time and EEG while performing a vigilance task during total sleep deprivation. *Sleep*, 1996. 19(7), p. 563-569.
33. Crick, F., and Mitchison, G., The function of dream sleep. *Nature*, 1983. 304, p. 111-113.
34. Dement, W.C., and Vaughan, C., *The Promise of Sleep*. 1999: Delacorte Press.
35. Donnell, J.M., Performance decrement as a function of total sleep loss and task duration. *Perceptual & Motor Skills*, 1969. 29, p. 711-714.
36. Dotto, L., *Asleep in the Fast Lane: the impact of sleep on work*. 1990: Stoddart Publishing co.
37. Drummond, S.P.A., Brown, G.G., Stricker, J.L., Buxton, R.B., Wong, E.C., and Gillin, J.C., Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *NeuroReport*, 1999. 10, p. 3745-3748.
38. Duteil, J., Rambert, F.A., Pessonnier, J., and Gombert, R., A possible alpha-adrenergic mechanism for drug (CRL 40028)-induced hyperactivity. *European Journal of Pharmacology*, 1979. 59, p. 121-123.
39. Eysenck, M.W., *Attention and arousal: Cognition and performance*. 1982, New York: Springer-Verlag.
40. Fairclough, S.H., and Graham, R., Impairment of driving performance caused by sleep deprivation or alcohol: A comparative study. *Human Factors*, 1999. 41(1), p. 118-128.
41. Ferraro, L., Antonelli, T., O'Connor, W.T., Rambert, F.A., and Fuxe, K., The vigilance promoting drug modafinil decreases GABA release in the medial preoptic area and in the posterior hypothalamus of the awake rat: Possible involvement of the serotonergic 5-HT₃ receptor. *Neuroscience Letters*, 1996. 220, p. 5-8.
42. Ferraro, L., Tanganelli, S., O'Connor, C., Antonelli, T., Rambert, F.A., and Fuxe, K., The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local gabaergic mechanism. *European Journal of Pharmacology*, 1996. 306, p. 33-39.
43. Ferraro, L., Antonelli, T., O'Connor, W.T., Tanganelli, S., Rambert, F.A., and Fuxe, K., Modafinil: An antinarcotic drug with a different neurochemical profile to d-amphetamine and dopamine uptake blockers. *Biological Psychiatry*, 1997. 42, p. 1181-1183.
44. Garbarino, S., Nobili, L., Beelke, M., De Carli Phy, F., and Ferrillo, F., The contributing role of sleepiness in highway vehicle accidents. *Sleep*, 2001. 24(2), p. 203-206.
45. Gavelek, J., and Raphael, T.E., Metacognition, instruction, and the role of questioning activities, in *Metacognition, Cognition, and Human Performance*, D.L. Forrest-Pressley, G.E. MacKinnon, and T.G. Waller, Editors. 1985, Academic: New York. p. 103-136.
46. Gillberg, M., and Akerstedt, T., Sleep loss and performance: No "safe" duration of a monotonous task. *Physiology and Behavior*, 1998. 64(5), p. 599-604.
47. Harris, D.A., Pegram, F.V., and Hartman, B.O., Performance and fatigue in experimental double-crew transport missions. *Aviation, Space, and Environmental Medicine*, 1971. 24, p. 980-986.
48. Harrison, Y., and Horne, J.A., Sleep deprivation affects speech. *Sleep*, 1997. 20(10), p. 871-877.
49. Harrison, Y., and Horne, J.A., One night of sleep loss impairs innovative thinking and flexible decision making. *Organizational Behavior and Human Decision Processes*, 1999. 78(2), p. 128-145.
50. Harrison, Y., and Horne, J.A., Sleep loss and temporal memory. *The Quarterly Journal of Experimental Psychology*, 2000. 53A(1), p. 271-279.
51. Harrison, Y., and Horne, J.A., The impact of sleep deprivation on decision making: A review. *Journal of Experimental Psychology: Applied*, 2000. 6(3), p. 236-249.

52. Hermant, J., Rambert, R.A., and Duteil, J., Awakening properties of modafinil: Effect on nocturnal activity in monkeys (*Macaca mulatta*) after acute and repeated administration. *Psychopharmacology*, 1991. 103, p. 28-32.
53. Heslegrave, R.J., and Angus, R.G., The effects of task duration and work-session location on performance degradation induced by sleep loss and sustained cognitive work. *Behavior Research Methods, Instruments & Computers*, 1985. 17(6), p. 592-603.
54. Hill, D.W., Welch, J.E., and Godfrey, J.A.I., Influence of locus of control on mood state disturbance after short-term sleep deprivation. *Sleep*, 1996. 19(1), p. 41-46.
55. Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., and Dement, W.C., Quantification of sleepiness: A new approach. *Psychophysiology*, 1973. 10, p. 431-436.
56. Horne, J.A., and Pettitt, A.N., High incentive effects on vigilance performance during 72 hours of total sleep deprivation. *Acta Psychologica*, 1985. 58, p. 123-139.
57. Horne, J.A., *Why We Sleep: The Functions of Sleep in Humans and Other Mammals*. 1988, Oxford: Oxford University Press.
58. Horne, J.A., Human sleep, sleep loss, and behaviour: Implications for the prefrontal cortex and psychiatric disorder. *British Journal of Psychiatry*, 1993. 162, p. 413-419.
59. Horne, J.A., and Foster, S.C. Can exercise overcome sleepiness? in *World Federation of Sleep Research Societies Second International Congress, The Mystery of Sleep*. 1995. Nassau, The Bahamas: Brain Information Service/Brain Research Institute.
60. Hughes, S., Drugged troops could soldier on without sleep, in *New Scientist*. 1991. p. 18.
61. Jeong, J., Kim, D., Kim, S.Y., Chae, J., Go, H.J., and Kim, K., Effect of total sleep deprivation on the dimensional complexity of the waking EEG. *Sleep*, 2001. 24(2), p. 197-202.
62. Johnson, L.C., Sleep deprivation and performance, in *Biological Rhythms, Sleep, and Performance*, W.B. Webb, Editor. 1982, John Wiley and Sons. p. 111-141.
63. Kavanau, J.L., Sleep and dynamic stabilization of neural circuitry: A review and synthesis. *Behavioural Brain Research*, 1994. 1994(63), p. 111-126.
64. Klein, G., A recognition primed decision (RPD) model of rapid decision making, in *Decision Making in Action: Models and Methods*, G.A. Klein, et al., Editors. 1993, Ablex: Norwood, N.J. p. 138-147.
65. Kleitman, N., *Sleep and Wakefulness*. 2nd edition ed. 1963, Chicago: University of Chicago Press.
66. Koslowsky, M., and Babkoff, H., Meta-analysis of the relationship between total sleep deprivation and performance. *Chronobiology International*, 1992. 9(2), p. 132-136.
67. Krueger, G.P., Sustained work, fatigue, sleep loss and performance: A review of the issues. *Work & Stress*, 1989. 3(2), p. 129-141.
68. Krueger, J.M., Obal, F.J., and Fang, J., Why we sleep: a theoretical view of sleep function. *Sleep Medical Review*, 1999. 3, p. 119-129.
69. Laffont, F., Cathala, H.P., and Kohler, F. Effect of modafinil on narcolepsy and idiopathic hypersomnia. in *the 5th European Congress of Sleep Research*. 1987.
70. Laffont, F., Agar, N., Minz, M., and Mayer, G., Spectral analysis of wakefulness and sleepiness in narcoleptic patients. *Journal of Sleep Research*, 1992. 1(supplement 1), p. 125.
71. Laffont, F., Mayer, G., and Minz, M., Modafinil in diurnal sleepiness. A study of 123 patients. *Sleep*, 1994. 17, p. S113-S115.
72. Lafon Laboratoire, Modiodal[®], Modafinil. Dossier d'information médicale et pharmaceutique. 1994.
73. Lagarde, D., Effects of modafinil on the nocturnal activity and behavioural sleep of Rhesus monkeys (*Macaca mulatta*). *Medical Science Research*, 1990. 18, p. 307-399.

74. Lagarde, D., F., L., and Matton, T., Gestion de la vigilance au cours des operations soutenues - Application au conflit du golfe persique. 1991, CERMA.
75. Lagarde, D., and Batejat, D., Disrupted sleep-wake rhythm and performance: Advantages of modafinil. *Military Psychology*, 1995. 7(3), p. 165-191.
76. LeDuc, P.A., Caldwell, J.A.J., and Ruyak, P.S., The effects of exercise as a countermeasure for fatigue in sleep-deprived aviators. *Military Psychology*, 2000. 12(4), p. 249-266.
77. Leger, D., The cost of sleep-related accidents: A report for the National Commission of Sleep Disorders Research. *Sleep*, 1994. 17(1), p. 84-93.
78. Lin, J., Gervasoni, D., Hou, Y., Vanni-Mercier, G., Rambert, F., Frydman, A., and Jouvet, M., Effects of amphetamine and modafinil on the sleep/wake cycle during experimental hypersomnia induced by sleep deprivation in the cat. *Journal of Sleep Research*, 2000. 9, p. 89-96.
79. Lorenzo, I., Ramos, J., Arce, C., Guevara, M.A., and Corsi-Cabrera, M., Effect of total sleep deprivation on reaction time and waking EEG activity in man. *Sleep*, 1995. 18(5), p. 346-354.
80. Lyons, T.J., and French, J., Modafinil: The unique properties of a new stimulant. *Aviation, Space and Environmental Medicine*, 1991. 62, p. 432-435.
81. McLellan, T.M., Ducharme, M., Canini, F., Moroz, D., Bell, D., Baranski, J.V., Gil, V., Buguet, A., and Radomski, M., Effect of modafinil on thermoregulation during sleep deprivation and exercise in a warm environment. (manuscript submitted for publication), 2001.
82. McNair, D., Lorr, M., and Droppelman, L., Manual for the Profile of Mood States. 1971, Educational and Industrial Testing Service: San Diego, California.
83. Mignot, E., Nishino, S., Guilleminault, C., and Dement, W.C., Modafinil binds to the dopamine uptake carrier with low affinity. *Sleep*, 1994. 17, p. 436-447.
84. Milhaud, C.L., and Klien, M.J., Effets de l'adrafinil sur l'activite nocturne du macaque Rhesus. *Journal of Pharmacology*, 1985. 16(4), p. 372-380.
85. Mitler, M.M., Gujavarty, K.S., and Browman, C.P., Maintenance of wakefulness test: A polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. *Electroencephalography and Clinical Neurophysiology*, 1982. 53, p. 658-661.
86. Mitler, M.M., Aldrich, M.S., Koob, G.F., and Zarcone, V.P., Narcolepsy and its treatment with stimulants. *Sleep*, 1994. 17(4), p. 352-371.
87. Naitoh, P., Pasnau, R.O., and Kollar, E.J., Psychophysiological changes after prolonged deprivation of sleep. *Biological Psychiatry*, 1971. 3, p. 309-320.
88. Newhouse, P.A., Penetar, D.M., Fertig, J.B., Thorne, D.R., Sing, H.C., Thomas, M.L., Cochran, J.C., and Belenky, G.L., Stimulant drug effects on performance and behavior after prolonged sleep deprivation: A comparison of amphetamine, nicotine and Deprenyl. *Military Psychology*, 1992. 4, p. 207-233.
89. Niedermeyer, E., Sleep and EEG, in *Electroencephalography: Basic Principles, Clinical Applications and Related Fields*, E. Niedermeyer and F. Lopes da Silva, Editors. 1982, Urban & Schwarzenberg: Baltimore-Munich. p. 93-105.
90. Philip, P., and Mitler, M., Sleepiness at the wheel: Symptom or behavior? *Sleep*, 2000. 23(4), p. S119-S121.
91. Pigeau, R., Angus, B., and O'Neill, P., Vigilance latencies to aircraft detection among NORAD surveillance operators. *Human Factors*, 1995. 37(3), p. 622-634.
92. Pigeau, R., Naitoh, P., Buguet, A., McCann, C., Baranski, J., Taylor, M., Thompson, M., and Mack, I., Modafinil, d-amphetamine, and placebo during 64 hours of sustained mental work I: Effects on mood, fatigue, cognitive performance, and body temperature. *Journal of Sleep Research*, 1995. 4(4), p. 212-228.
93. Pigeau, R.A., Angus, R., and Heslegrave, R.J. Electrophysiological measures of mental fatigue and declining performance resulting from sleep loss. in *Proceedings of the 29th Military Testing Association Conference*. 1987. Ottawa, Canada.

94. Pigeau, R.A., Heslegrave, R.J., and Angus, R. Psychophysiological measures of drowsiness as estimators of mental fatigue and performance degradation during sleep deprivation. in *Proceedings of the Aerospace Medical Panel Symposium, Electric and Magnetic Activity of the Central Nervous System: Research and Clinical Applications in Aerospace Medicine*. 1987. Trondheim, Norway.
95. Pigeau, R.A., and Naitoh, P. The effect of modafinil and amphetamine on core temperature and cognitive performance using complex demodulation during 64 hours of sustained work. in *Proceedings of the 80th Annual Meeting/Symposium of the Aerospace Medical Panel on Neurological Limitations of Aircraft Operations: Human Performance Implications. AGARD Conference Proceedings No. 579*. 1995. Koeln, Germany.
96. Pigeau, R.A., and Angus, R.G., Modafinil and amphetamine versus naps in sustained operations, in *Countermeasures for Battlefield Stressors*, K. Friedl, et al., Editors. 2000, Louisiana State University Press: Baton Rouge. p. 206-227.
97. Pilcher, J.J., and Huffcutt, A.I., Effects of sleep deprivation on performance: A meta analysis. *Sleep*, 1996. 19(4), p. 318-326.
98. Rambert, F.A., Pessonnier, J., de Sereville, J.E., Pointeau, A.M., and Duteil, J., Profil psychopharmacologique original de l'adrafinil chez la souris. *Journal of Pharmacology*, 1986. 17, p. 37-52.
99. Ray, C., Weir, W.R.C., Phillips, S., and Cullen, S., Development of a measure of symptoms in chronic fatigue syndrome: the Profile of Fatigue-Related Symptoms (PFRS). *Psychological Health*, 1992. 7, p. 27-43.
100. Rechtschaffen, A., and Kales, A., A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. 1968, Public Health Service, U.S. Government Printing Office: Washington, D.C.
101. Redmond, D.P., Sing, H.C., and Hegge, F.W., Biological time series analysis using complex demodulation, in *Rhythmic Aspects of Behavior*, F.W. Brown and R.C. Graeber, Editors. 1982, Erlbaum: Hillsdale, NJ. p. 429-457.
102. Saletu, B., Grunberger, J., Linzmayer, L., and Stohr, H., Pharmaco-EEG, psychometric and plasma level studies with two novel alpha-adrenergic stimulants CRL 40476 and 40028 (Adrafinil) in elderly. *New Trends in Experimental and Clinical Psychiatry*, 1986. 2, p. 5-31.
103. Shelton, J., Nishino, S., Vaught, J., Dement, W.C., and Mignot, E., Comparative effects of modafinil and amphetamine on daytime sleepiness and cataplexy of narcoleptic dogs. *Sleep*, 1995. 18(10), p. 817-826.
104. Sing, H.C., Thorne, D.R., Hegge, F.W., and Babkoff, H., Trend and rhythm analysis of time-series data using complex demodulation. *Behavior Research Methods, Instruments & Computers*, 1985. 17, p. 623-629.
105. Thomas, M., Sing, H.C., Belenky, G., Holcomb, H., Mayberg, H., Dannals, R., Wagner Jr., H., Thorne, D., Popp, K., Rowland, L., Welsh, A., Balwinski, S., and Redmond, D., Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research*, 2000. 9, p. 335-352.
106. Walsh, J.K., and Lindblom, S.S., Psychophysiology of sleep deprivation and disruption, in *Understanding sleep: The Evaluation and Treatment of Sleep Disorders*, M.R. Pressman and W.C. Orr, Editors. 1997, American Psychological Association: Washington. p. 73-110.
107. Webb, W.B., The cost of sleep-related accidents: A reanalysis. *Sleep*, 1995. 18(4), p. 276-280.
108. Wilkinson, R.T., The measurement of sleepiness, in *Sleep, Arousal and Performance*, R.J. Broughton and R.D. Ogilvie, Editors. 1992, Birkhauser: Boston. p. 254-265.
109. Williams, H.L., Lubin, A., and Goodnow, J.J., Impaired performance with acute sleep loss. *Psychological Monographs (No. 484)*, 1959. 73, p. 1-26.