

## SLEEP, WAKING AND NEUROBEHAVIOURAL PERFORMANCE

Naomi L. Rogers, Jillian Dorrian, David F. Dinges

*The University of Pennsylvania School of Medicine, Unit for Experimental Psychiatry, Division of Sleep and Chronobiology, 1013 Blockley Hall, 423 Guardian Drive, Philadelphia, PA*

### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Control of waking function
4. Sleep deprivation and waking neurobehavioural functioning
  - 4.1. Total sleep deprivation
  - 4.2. Partial sleep deprivation
5. Possible mechanisms underlying neurobehavioural performance deficits during sleep loss
6. Countermeasures to neurobehavioural deficits associated with sleep loss
  - 6.1. Naps
    - 6.1.1. Laboratory studies
    - 6.1.2. Prophylactic napping
    - 6.1.3. Field studies
  - 6.2. Sleep inertia
  - 6.3. Rest breaks as a potential countermeasure
  - 6.4. Wake promoting compounds
    - 6.4.1. Caffeine
    - 6.4.2. Caffeine plus
    - 6.4.3. Modafinil
7. Summary
8. Acknowledgments
9. References

### 1. ABSTRACT

Waking neurobehavioural or cognitive functioning is largely dependent on two mechanisms both in synchrony and in opposition to each other: the sleep homeostatic and circadian systems. The influences of these systems are particularly evident during periods of sustained wakefulness or sleep deprivation. Although the effects of these two systems on neurobehavioural functioning during periods of extended wakefulness have been demonstrated experimentally, there does not exist an adequate theory to describe the underlying brain mechanisms responsible for these neurobehavioural deficits. Much research has in fact concentrated not on understanding the nature of these deficits, but rather in counteracting them, via the use of countermeasures, such as naps and wake promoting compounds.

### 2. INTRODUCTION

Sleep is an active behaviour, which is a reversible, repeating state of unconsciousness that can only be resisted for a limited period of time. Although the exact function(s) of sleep have yet to be determined, it has been hypothesised that during sleep tissue repair and growth, learning or memory consolidation, and restorative processes are occurring throughout the brain and the body (for review see 1-3). Therefore, it is reasonable to conclude that sleep does not have one single function, but rather that

it is a time during which a number of necessary neurobiological, physiological and behavioural processes are occurring. Conversely, during sleep deprivation, either total or chronic partial, significant detrimental effects on physiology, e.g. decreased immune function (for review see 3, 4), decreased glucose tolerance (5); and on neurobehavioural functioning, e.g., decreased cognitive and memory functions, decreased motor skills, increased sleepiness and fatigue (e.g., 5-7) have been reported. Further, it is evident that the physiological need for sleep created by sleep loss can only be reversed by sleep.

This paper will briefly describe normal waking neurobehavioural functioning, as exhibited following adequate sleep, and how this may be modified by alterations in the sleep homeostatic and circadian systems – using sleep deprivation as an experimental paradigm; provide some examples of real world situations where the impact of sleep deprivation is felt, and present possible hypotheses to explain the nature of these changes in neurobehavioural functioning.

### 3. CONTROL OF WAKING FUNCTION

The physiological and behavioural activities of humans are influenced by the interaction of a number of forces, the two strongest being the circadian and sleep

## Sleep loss & neurobehavioural function

homeostatic systems. Other factors that influence these activities include posture, activity (e.g., exercise), noise, light levels and mood.

The central circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus (9, 10), is responsible for the generation of circadian rhythms in the physiological, neurobiological and behavioural systems under its control, to achieve coordinated functioning throughout the brain and body. The circadian pacemaker is entrained to the twenty-four hour Earth day via external time cues from the environment, termed zeitgebers (11). The most salient of these time cues is the light-dark cycle. Via entrainment to the twenty-four hour day, the circadian system achieves a balance between the timing of endogenous activities by the individual and the external environment, such that sleeping and waking, hormonal secretions, temperature fluctuations and neurobehavioural functioning all occur in synchrony with the environment.

The circadian system plays an important role in regulating the timing of sleep-wake behaviour, not only dictating the optimal time for sleep and waking to occur, but also influencing the duration of sleep periods, and the underlying sleep structure. Despite the strong influence on sleep activity, the circadian system is often defined as a wake promoting system. Acting in opposition to the wake drive produced by the circadian system is the sleep homeostatic system. The sleep drive strongly influences sleep propensity, and also sleep structure [especially evident following extended periods of wakefulness] (for review see 12).

During periods of sleep deprivation, the homeostatic drive for sleep, or sleep need, increases, producing an increased likelihood for sleep onset to occur, with an associated decrease in alertness and increase in fatigue levels. In addition to this escalating sleep need is the twenty-four hour variation in wake drive produced by the circadian system, which produces peaks and troughs in sleepiness and alertness across the day. Therefore, the magnitude of the sleepiness or alertness experienced at any given time is determined by summing the influences of these two systems. Consequently, it is possible to be more alert at certain times of the day later in a period of sleep deprivation, relative to other periods (e.g., during the normal nocturnal sleep period) that occur with less time awake.

In addition to influencing sleepiness and alertness, both the circadian and sleep homeostatic systems have profound effects on daily fluctuations in neurobehavioural functioning. Circadian rhythmicity has been demonstrated in a number of neurobehavioural variables, including: vigilance, arithmetic, serial search tasks, choice reaction time, cognitive throughput, short-term memory, (13-17). The circadian variation in neurobehavioural performance measures appears to be temporally related to the daily fluctuation in core body temperature (17-21). When core body temperature is high, neurobehavioural performance and alertness levels are also

high, with reduced levels of neurobehavioural performance and alertness associated with low body temperatures. Further, it is when core body temperature is low that sleep propensity is high.

## 4. SLEEP DEPRIVATION AND WAKING NEUROBEHAVIOURAL FUNCTIONING

During periods of sleep deprivation, both total and partial, the combined influences of the circadian and sleep homeostatic systems become particularly evident.

### 4.1. Total Sleep Deprivation

Since the first study investigating sleep deprivation and human performance in 1896 (22), there has been extensive research into the neurobehavioural effects of total sleep deprivation. With increasing time awake an elevated drive for sleep ultimately leads to uncontrolled incidences of sleep, or sleep attacks. These sleep periods may take the form of 'microsleeps' lasting for seconds, or may occur for longer periods of time. Intrusions of sleep into the waking state of sleep-deprived individuals is associated with a reduction in behavioural responsiveness or the absence of a response, or performance lapse. Even before sleep onset occurs, reductions in performance capability are observed.

Experimentally induced sleep deprivation studies have provided evidence that a wide variety of neurobehavioural performance measures are affected by sleep loss. For example, sleep deprivation deficits in reaction time (23, 24), vigilance (25), sustained attention (8), mental arithmetic (23), short-term recognition memory (26, 27), logical reasoning (24, 28), tracking ability (28, 29), word generation, vocal intonation (30) and mood (23) have been reported by numerous researchers.

Since neurobehavioural performance is affected by both the homeostatic drive for sleep and the circadian phase at which it occurs, sleep deprivation induced deficits in performance do not occur simply in a linear fashion (20, 23, 29). During sleep deprivation, the resulting pattern of performance degradation reflects both a linear component due to the homeostatic sleep system combined with a circadian pattern of performance variation. Furthermore, with increasing time awake, the escalating drive for sleep amplifies the circadian performance rhythm such that over successive days, the level of impairment at the nadir of the rhythm becomes greater (24, 31).

### 4.2. Partial Sleep Deprivation

Despite the widespread occurrence in the general population of restricted sleep schedules, producing chronic partial sleep deprivation, few studies have comprehensively investigated the effects of chronic partial sleep deprivation on neurobehavioural functioning in humans.

Early studies, conducted outside a controlled laboratory setting, typically reported no detrimental effects of chronic sleep restriction on aspects of neurobehavioural functioning. When sleep was reduced to between 4.3 hours to 6 hours per night for periods up to 8 months in duration,

## Sleep loss & neurobehavioural function

no significant effects on sleepiness (32), vigilance performance (31-34), psychomotor performance (35), addition, working memory or grip strength (33) were found. In addition, Webb and Agnew (33) reported no effect of sleep restriction on mood parameters. In contrast, however, Friedman *et al.*, (35) reported increased levels of subjective discomfort, sleepiness and impaired vigilance. Since these studies were conducted outside a controlled laboratory setting, contaminating factors, such as the level of napping and extension of sleep periods by subjects could not be well controlled.

In studies where the effects of sleep restriction were examined under controlled laboratory conditions, however, impairment of neurobehavioural functioning and subjective assessments of sleepiness were evident. In a study on daytime performance following one night of sleep restriction, with subjects allowed 1-5 hours time in bed (TIB), a decrease in auditory vigilance performance, and a linear increase in sleep propensity during multiple sleep latency test (MSLT) assessment and subjective sleepiness was evident (36). When nights of sleep restriction were extended beyond one night, cumulative increases in subjective and objective sleepiness (37-39) and vigilance performance were observed (38, 39). Comparison of data from subjects allowed 5 hours TIB for sleep for 7 nights and assessed during the day for levels of objective sleepiness (37) or neurobehavioural functioning using a sustained attention task (38) revealed a high correlation ( $r = -0.95$ ) between these two measures of alertness across days of chronic sleep restriction, from studies completed more than 15 years apart (38). This finding suggests a high degree of stability in the response of subjects to chronic periods of sleep restriction.

There are few studies that have carefully examined the effects of greater than 7 days of sleep restriction on neurobehavioural functioning. Recent studies from Dinges and colleagues have begun to investigate the effects of 10 and 14 days of chronic sleep restriction, with sleep placed both nocturnally and diurnally, out of phase with the normal circadian cycle of sleep-wake activity. Preliminary findings further demonstrate the cumulative nature of chronic sleep restriction, with subjects allowed between 4 and 8 hours TIB for sleep during each 24-hour period (40-43).

Comparison with studies of total sleep deprivation revealed that 4 hours of TIB for sleep per night for 14 nights produced performance decrements equivalent to that those observed when someone goes without sleep for more than 48 hours. In fact, when subjects lived on 4 hours TIB for sleep for only 3 nights, they were performing equivalent to someone who had been awake for 24 hours (43).

The performance deficits observed when subjects were performing across the night and attempting to sleep during the day followed a similar cumulative pattern of decrement to when subjects are sleeping at night. The magnitude of the neurobehavioural impairment was

significantly greater, however, reflecting a combined influence of the homeostatic and circadian systems (42).

## 5. POSSIBLE MECHANISMS UNDERLYING NEUROBEHAVIOURAL PERFORMANCE DEFICITS DURING SLEEP LOSS

The underlying mechanisms that produce deficits in neurobehavioural and cognitive functioning have yet to be fully elucidated. Several theories exist, however, that attempt to explain the changes in performance that occur during periods of sleep loss. One early theory was termed the lapse hypothesis (44). According to this theory, transient, short duration lapses in attention and performance occur during sleep deprivation, which are interspersed among periods of optimal performance and alertness.

While several authors have noted performance lapses during sleep deprivation (e.g., 21, 22, 44-48), decreased performance has also been observed between these extreme occurrences of neurobehavioural dysfunction. For example, more global decreases in performance, such as a reduction in fastest reaction times on vigilance tasks (48, 49) and an increased variability in reaction times across a task (51) have been reported. These findings suggest a more complex interaction between sleep loss and neurobehavioural performance than what the lapse hypothesis proposes.

One explanation for the increased variability in performance across the duration of a performance task, for example a 10 minute sustained attention task, may be a reflection of state instability (1, 51). This state instability is a result of the sum of performance lapses and a compensatory increase in effort, especially in highly motivated subjects. The performance lapses may be defined as errors of omission – a non-response. When subjects identify their poor performance and lapses of attention, they attempt to compensate and increase their rate of response, and produce both ‘normal’ responses and errors of commission – responding in the absence of the stimulus.

Recently, considerable attention has been focused on the potential mechanisms underlying neurocognitive performance, and the brain areas from which they are controlled, to provide an explanation of how sleep loss affects neurobehavioural function. One important area of the brain that is fundamental to neurobehavioural functioning is the prefrontal cortex. A number of performance tasks thought to be putatively subserved by the prefrontal cortex have been reported to demonstrate significant impairment during sleep loss – both total and chronic partial, that is reversible following recovery sleep (29, 51-53).

In addition to behavioural outputs of the prefrontal cortex demonstrating changes during sleep loss, increased activation of the frontal areas is evident during sleep loss also. Brain imaging during performance on cognitive tasks when subjects were sleep deprived had illustrated activation of prefrontal cortical regions (54-58).

## Sleep loss & neurobehavioural function

Furthermore, imaging studies have demonstrated decreased prefrontal activation associated with decreased performance on arithmetic tasks during sleep deprivation, relative to following adequate sleep (60-62).

It has been suggested, however, that activation and deactivation of cortical regions may reflect task specific effects during sleep loss (63). In contrast to the arithmetic task, learning and divided attention tasks produced increased levels of cortical activation following one night without sleep compared to one night with sleep (60). Moreover, a positive relationship between increased levels of sleepiness and increased prefrontal activation was reported. It is possible that this differential activation of the prefrontal cortex may represent compensatory effort to perform under conditions that are not conducive to optimal performance – i.e. sleep deprivation-induced sleepiness and fatigue.

One important factor that may influence the ability to perform the majority, if not all, neurobehavioural tasks is working memory, or sustained attention. It can be argued that without the ability to maintain either of these variables, if they are indeed two separate variables, neurocognitive functioning is severely impaired or impossible to achieve. It has been suggested that a central executive, or central attentional system (64, 65) controls working memory. Supervisory, or executive attention has been described as a primary aspect of working memory (66).

Performance on working memory tasks has been reported to predict performance on a range of other tasks of cognitive function (66). Consequently, it has been argued that performance on working memory tasks reflects a fundamental aspect of cognition. If this hypothesis is correct, it may provide an explanation of why simple monotonous tasks that rely heavily on high levels of sustained attention and working memory are more sensitive to sleep loss than more complex tasks that require a higher level of cognition in addition to these basic functions.

Interestingly, brain-imaging studies have demonstrated a relationship between working memory and the prefrontal cortex (56, 67-70). Furthermore, the prefrontal cortex has also been implicated in the maintenance of sustained attention (66). Hence, the observed link between sleep deprivation and reduced neurobehavioural performance on 'prefrontal' tasks may represent impairments of sustained attention.

### 6. COUNTERMEASURES TO NEUROBEHAVIOURAL DEFICITS ASSOCIATED WITH SLEEP LOSS

Despite the acknowledgement that adequate sleep is necessary for optimal waking functioning, people are always looking for ways to 'cheat the system'. Consequently, countermeasure development and assessment is an important and active area of current research. Intervention countermeasures to neurobehavioural deficits associated with sleep loss and fatigue include naps and administration of wake promoting compounds.

### 6.1. Naps

Investigations into the effectiveness of naps as a countermeasure to sleep deprivation induced neurobehavioural deficits may be divided into three categories: in-laboratory studies of naps, prophylactic naps and field studies.

#### 6.1.1. Laboratory studies

The majority of studies investigating the effectiveness of napping as a countermeasure to sleep deprivation have been performed under controlled laboratory conditions. Naps have been investigated in the context of both total sleep deprivation and sleep restriction. Several authors have reported an increase in neurobehavioural performance following naps of durations ranging between 15 minutes and 2 hours during total sleep deprivation of between 36 to 88 hours (28, 70-72). The effects of naps on subjective reports during sleep deprivation are less clear. While some authors have reported little or no subjective alerting effects of naps (71, 72), others find elevated alertness levels following naps (73, 74).

The benefits of naps on neurobehavioural functioning following periods of restricted sleep have also been explored. Following one night of sleep restricted to a 4 or 5 hour opportunity, naps of 10 or 30 minutes (75), 15 minutes (76) or 60 minutes (77) produced an increase in neurobehavioural functioning and objective measures of alertness. Interestingly, Tietzel and Lack, (75) also reported an increase in subjective alertness for up to 60 minutes following the termination of a 10-minute nap.

In a recently completed study, Dinges and colleagues investigated the effects of diurnally placed naps to supplement nocturnally restricted sleep for a period of 10 days (41, 78). When comparing neurobehavioural functioning following an 8.2h nocturnal sleep opportunity each night with that following a 4.2h sleep opportunity, daily naps with at least 48 minutes (up to 144 minutes) allowed for sleeping were found to increase neurobehavioural performance above what was observed when naps were of a shorter duration (24 minutes). These naps, however, were not able to reverse the effects of restricted sleep on cognitive performance, with performance in the 8.2h group always remaining above that of subjects allowed only 4.2h sleep opportunity each night, irrespective of nap duration.

In the studies of total sleep deprivation and naps, both Dinges *et al.*, (71) and Mullaney *et al.*, (29) reported an increased effectiveness of naps placed early in the period of sleep deprivation, before a significant sleep debt had accumulated. These naps were termed prophylactic naps, and several studies have concentrated on the beneficial effects of these.

#### 6.1.2. Prophylactic napping

Several researchers have reported on the positive effects of naps on subsequent performance, when the nap is placed prior to the build up of a sleep debt – i.e. prophylactic naps (71). The beneficial effects of

## Sleep loss & neurobehavioural function

prophylactic naps, taken prior to accumulation of a significant sleep debt, may not be evident until several hours post nap, especially if a significant period of sustained wakefulness follows the nap (e.g., 71, 79). For example, a 4 hour nap taken in the evening prior to a night of sleep deprivation has been demonstrated to increase neurobehavioural functioning across that night, and in particular across the circadian nadir when neurobehavioural performance is typically at its lowest (80).

Naps taken earlier in a period of sleep deprivation, with only a mild accumulation of sleep debt, also produced significant beneficial effects. Following a 2-hour nap taken 6 hours after awakening, an increase in neurobehavioural functioning was evident during a subsequent period of sleep loss (71, 79). Further, a greater benefit was observed following this nap relative to naps taken after a greater period of wakefulness (after 18, 30, 42 or 54 hours awake). Although an improvement in neurobehavioural functioning was evident, there was no effect of the prophylactic nap, or any subsequent naps, on subjective assessments of sleepiness. This finding illustrates the divergence of objective versus subjective assessments during sleep deprivation, which have been reported previously, under conditions of total and partial sleep loss (71).

Not only may the timing of the prophylactic nap be important, but also the duration of the nap allowed. Bonnet and colleagues (81-83) reported dose dependent increases in neurobehavioural performance following prophylactic naps of varying lengths (0, 2, 4 and 8h) during 52 hours or 1 night of total sleep deprivation. Further, Gander *et al.*, (84) reported that a prophylactic nap of between 2 and 4 hours duration produced an increase in neurobehavioural alertness, measured using the multiple sleep latency test, equivalent to that reported following 150-300mg caffeine; and the 8 hour nap was equal to a 400mg dose of caffeine.

### 6.1.3. Field studies

Previous studies have reported that flight crews often experience uncontrolled sleep attacks during flight (84-86). In addition, there have been reports of decreased performance levels, with lapses and brief sleep periods during long haul night flights (87). In 1993 an advisory committee to the FAA in America suggested introducing a federal regulation that would allow planned napping on planes with a crew of 3 members (e.g. Boeing 747). SwissAir already allows for some napping by its flight crews.

A small number of studies have investigated the effects of naps during sleep deprivation in field rather than laboratory settings. Given that the majority of these studies have been conducted as part of military training exercises, sleep deprivation is not the only variable likely to induce deficits in neurobehavioural functioning and fatigue levels. Consideration must also be given to the effects of physical exercise, caloric restriction and the added stress of performance expectations.

Following 4 days of sustained wakefulness, coupled with physical exercise during military training exercises, naps of 6 and 3 hours in duration were able to increase neurobehavioural performance (88), although performance levels were not returned to baseline levels. In addition, the increase in neurobehavioural performance following the nap was associated with an increase in mood (89). In a further study, subjects exposed to a 9 day training exercise demonstrated a dose related benefit of sleep, with subjects receiving 3 hours/24 hours tolerating the training exercise better than subjects who received either 90 minutes/24 hours or no sleep at all (90). In fact, by the fourth day, all subjects in the zero sleep condition had withdrawn from the training exercise, and only 50% of those subjects allowed 90 minutes of sleep per day finished (91% of the 3 hour group finished). Although the subjects in the 3-hour sleep group reported a lower level of subjective sleepiness relative to the 90-minute sleep group, there was no difference in neurobehavioural performance levels between the 2 groups.

### 6.2. Sleep inertia

One negative aspect of napping as a countermeasure to neurobehavioural deficits during sleep deprivation, is the groggy feeling, with increased levels of sleepiness and reduced levels of neurobehavioural functioning that occurs immediately following termination of sleep. Upon awakening, neurobehavioural performance may actually be lower than prior to the commencement of the sleep period. In 1963, Kleitman (23) reported that "immediately after getting up, irrespective of the hour, one is not at one's best" (p. 124). This feeling was later termed sleep inertia. This phenomenon has been reported to last anywhere from a few minutes (91, 92) up to a few hours (93).

Effects of sleep inertia are evident in a number of neurobehavioural variables including simple and complex reaction time (94-100); visual perceptual tasks (101); memory (102-104); time estimation (105); mental addition, subtraction, decoding and reasoning (90, 94, 106-108); decision making (109); logical reasoning (91).

Studies have suggested that the intensity and duration of sleep inertia are dependent on sleep depth or intensity (e.g., 109), sleep duration (e.g., 93), the time of day (e.g., 110) and the sleep stage from which subjects were awoken (e.g., 108). There are inconsistencies regarding the effect of the circadian system on sleep inertia, however. Medical conditions may also affect the dynamics of sleep inertia. Chugh *et al.*, (111) reported that patients with obstructive sleep apnea syndrome (OSAS) experienced changes in sleep infrastructure that were independent of respiratory disturbance and rate of arousals during sleep. The chronic fragmentation of sleep found in patients with OSAS produces an increased homeostatic pressure for sleep, and an increase in the severity of sleep inertia. This effect on sleep inertia was reported to be equivalent in OSAS patients and experimental subjects awoken across the night.

## Sleep loss & neurobehavioural function

The time taken to recover from sleep inertia is not equivalent for all neurobehavioural variables. For example, tasks requiring use of gross motor skills, e.g. reaction time tasks, have a relatively rapid rate of recovery. Other more complex tasks, such as mental arithmetic and complex simulations, take a greater amount of time to recover. It appears that performance accuracy is more affected by sleep inertia relative to speed of performance (95, 96). Despite what is understood regarding the dynamics of sleep inertia, little is known about ways to reduce or alleviate this post-sleep decrement in neurobehavioural performance. Tassi *et al.*, (104) reported that noise was able to eliminate sleep inertia following a 1-hour nap taken at 0100h, but not at 0400h. This finding was likely due to masking effects of the noise on performance at 0100h, that were insufficient to overcome the effects of sleep inertia around the time of the circadian nadir (0400h).

Several researchers have developed mathematical models of neurobehavioural functioning and alertness, based on experimental data collected under controlled laboratory conditions. In one model, the three main components that described these functions included: a homeostatic component, a circadian component and a sleep inertia component (93). In this model, the sleep inertia component rises in a saturating exponential manner following waking. This is consistent with reports by Achermann *et al.*, (112), who described the time course of sleep inertia for both subjective alertness and objective performance measures using an exponential function.

In a subsequent report, Jewett *et al.*, (93) described mathematical models to predict sleep inertia changes in subjective alertness and objective neurobehavioural performance (cognitive throughput). Alertness and neurobehavioural performance measures from the first 4 hours following awakening from an eight-hour sleep period, on three consecutive days were used in the model development. Sleep inertia decreased in an asymptotic manner, and took between 2-4 hours to reach a trough. In addition, subjective alertness and performance decrements were equivalent whether subjects were allowed to rise from bed, eat breakfast, shower, and be exposed to normal room lighting levels (approximately 150 lux) or whether subjects were part of a constant routine protocol, where they were required to remain in bed, eat small snacks at hourly intervals and were exposed to dim lighting levels (10-15 lux). In contrast to Tassi *et al.*, (104), these findings suggest a lack of effect of environmental conditions on sleep inertia effects on both subjective alertness and objective performance measures.

### 6.3. Rest breaks as a potential countermeasure

Several studies have investigated the effectiveness of rest breaks as opposed to naps as potential countermeasures to sleep deprivation-induced neurobehavioural deficits. Only resting and not sleeping would avoid the effects of sleep inertia. These studies, however, have produced mixed results.

Heselgrave and Angus (113) reported higher levels of neurobehavioural performance directly following a rest break, relative to performance bouts placed later in testing sessions during 54 hours sleep deprivation. Similarly, Pigeau *et al.*, (114) reported increased performance and alertness following rest breaks during 64 hours of sleep deprivation. Increases in neurobehavioural performance due to rest periods during longer duration performance tasks, e.g., 1 hour driving simulation, have also been reported (115, 116), however, these increases were transient, and of a smaller magnitude than those resulting from caffeine administration.

Recently, the effects of mild physical activity as a countermeasure to fatigue in flight during a 6-hour simulated nighttime flight were reported (117). Subjects were allowed five short (7min) breaks at hourly intervals throughout the flight, with mild physical activity or one short (7min) break in the middle of the flight.

Subjects allowed multiple breaks experienced decreased physiological sleepiness and number of sleep episodes, relative to control subjects allowed one break. Similar to work by Horne and Reyner (115), the beneficial effects of the break periods were transient. Despite the positive effect on sleepiness, these rest breaks had no effect on neurobehavioural performance.

Taken together, these findings suggest only a short term, transient benefit of rest breaks on sleepiness levels, with limited or no effect on neurobehavioural performance. Thus, rest breaks may not actually reverse the fatigue-inducing effects due to performing during extended wakefulness, but merely mask them. Consequently, rest breaks should not be considered an acceptable alternative to naps or sleep breaks, despite the lack of sleep inertia related effects.

### 6.4. Wake Promoting Compounds

While the only true countermeasure to the neurobehavioural deficits associated with sleep loss is adequate sleep itself, wake promoting compounds are widely administered in an attempt to maintain performance levels in the face of fatigue associated with sleep need. Several studies have investigated the performance promoting effects of compounds such as amphetamine during sustained operations or sleep deprivation studies. Although compounds such as amphetamine have been widely demonstrated to increase alertness and neurobehavioural functioning levels (114, 118-120), significant side effects have been associated with their administration. These side effects, including increased locomotor agitation, negative effects on subsequent sleep episodes, and the potential for addiction, have meant that compounds such as amphetamine are not widely endorsed as acceptable countermeasures to the neurobehavioural and alertness deficits associated with sleep deprivation and sustained operations. Other compounds that have also been widely studied, both in laboratory and real world situations, and that are associated with fewer side effects, include caffeine and modafinil.

## Sleep loss & neurobehavioural function

### 6.4.1. Caffeine

Caffeine is one of the most widely accepted and administered alertness promoting compounds. In addition to its extensive use by the general public, numerous laboratory-based studies have investigated the effects of this compound on neurobehavioural performance and alertness, in both sleep satiated and sleep deprived subjects.

In the majority of studies examining the effects of caffeine on diurnal performance following a normal night of sleep, an increase in objective measures of performance (120-135) and subjective assessments of energy levels and alertness (129, 130, 136) was reported. Similar findings have also been reported following restricted sleep schedules. Rosenthal and colleagues (125) reported a significant increase in alertness levels following administration of caffeine (75 or 150mg) following either an 8 hour or 5 hour (restricted) sleep period; as did Lumley *et al.*, (126) with 4.0mg/kg caffeine following 5, 8 or 11 hours time in bed; and DeValck and Cluydts, (127) reported an improvement in driving performance on a simulator following a restricted sleep schedule. During total sleep deprivation studies, caffeine administration has been reported to decrease subjective sleepiness and fatigue (121), increase objective alertness, measured using the multiple sleep latency test (82, 129, 130, 140, 141), increase mood (130) and increase performance on a number of neurobehavioural tasks, including sustained attention (72, 131), divided attention (123), vigilance (123), mental arithmetic (132), logical reasoning (132), choice reaction time (133) and memory (72).

### 6.4.2. Caffeine plus

A small number of studies have examined the effectiveness of caffeine as an alerting agent during sleep deprivation in combination with an additional countermeasure: naps or bright light exposure. The combination of prophylactic naps and caffeine during twenty-four hours of sleep deprivation was reported to produce an improvement in neurobehavioural functioning, cognitive performance and alertness across the night (82, 132, 134).

Recently, Dinges and colleagues (72, 131) investigated the effects of naps (2 hours every 12 hours) with and without sustained low dose caffeine (0.3mg/kg/h for 66 hours) during 88 hours of sleep deprivation (simulated sustained operations) in a double blind, placebo controlled study. Relative to subjects receiving placebo and no naps, caffeine produced a significant increase in cognitive performance, for approximately 22 hours - coinciding with the rising portion of the plasma caffeine pharmacokinetic curve. When subjects were allowed the two naps per 24 hours in combination with sustained low dose caffeine, a greater improvement in cognitive performance was evident. Further, caffeine administration was found to significantly reduce the effects of sleep inertia on cognitive performance following termination of the naps (135).

Wright *et al.*, (136) examined the effects of bright light exposure and caffeine administration to improve

performance and alertness levels during 45.5h of sleep deprivation. The combination of caffeine with bright light exposure produced the greatest levels of alertness and cognitive performance, relative to dim light exposure with and without caffeine, and bright light exposure with placebo.

### 6.4.3. Modafinil

The wake promoting compound modafinil is currently approved for use in treating excessive daytime sleepiness associated with narcolepsy. In addition, several laboratory studies have assessed the effectiveness of this compound in overcoming the sleep deprivation-induced deficits in neurobehavioural functioning and alertness.

The exact mechanism of action for modafinil's wake promoting effects has yet to be fully described. In direct comparisons with other wake promoting compounds, modafinil has been demonstrated to be associated with fewer of the adverse events typically associated with stimulants like amphetamines, such as locomotor agitation and sleep disturbance. In addition, reports suggest that subjectively modafinil is more similar to caffeine than amphetamine (137).

Pigeau and colleagues reported on the ability of modafinil (300mg) to improve reaction time, logical reasoning and short-term memory performance and decrease subjective feelings of fatigue and sleepiness during 64 hours of total sleep deprivation (114, 138). In addition, increased performance on reaction time (139, 140), grammatical reasoning (139), sustained attention (140) and visual search tasks (141) and increased objective and subjective alertness (140) following the administration of modafinil during total sleep deprivation have been reported. During a simulated defense mission protocol with extended wakefulness and restricted sleep periods, and increase in memory, tracking and dual task performance was reported following administration of 200mg modafinil (142). When the modafinil administration was combined with a nap sleep period, an increase in arithmetic and tracking performance was also observed.

Several studies have compared the effects of modafinil to those of amphetamines in maintaining performance levels during sleep deprivation. Modafinil has been reported to be associated with fewer sleep disturbances relative to amphetamine during recovery sleep periods following sleep deprivation and drug administration (143). In addition, Edgar and Seidel have demonstrated that, unlike other psychostimulants, modafinil reduced rebound sleepiness in various animal models, and appeared to reduce the requirement for recovery sleep (144). This finding is similar to Pigeau *et al.*, (114), where it appeared that subjects receiving modafinil required shorter durations of recovery sleep following sleep deprivation.

Positive effects of modafinil administration during simulated shiftwork studies, where subjects were required to sleep during the day and remain awake and active throughout the night have also been reported. Compared to subjects receiving placebo, those in the

## Sleep loss & neurobehavioural function

modafinil (200mg) group reported increased subjective alertness levels and performed better on a sustained attention task (145). Further, there was no disruption of the daytime sleep periods associated with administration of modafinil.

In addition to the positive effects of modafinil, a small number of studies have reported mild adverse effects, with decreased efficiency of communication (146) and decreased subjective estimates of cognitive capability (147). In a study of helicopter pilots completing simulated maneuvers during 40 hours of wakefulness with three 200mg doses of modafinil or placebo, an increase in anecdotal reports of vertigo, nausea, and dizziness was reported (119). It was unclear from the study whether these side effects were due to the flight simulators or modafinil.

## 7. SUMMARY

Waking neurobehavioural functioning is highly dependent on the interaction of the homeostatic and circadian systems. The degree of neurobehavioural impairment observed in experimental studies of sleep deprivation – both total sleep deprivation and partial sleep loss or restriction – is determined by the time of day at which performance is undertaken, prior wakefulness, and the summation of these two factors. While it is often desirable to attempt to overcome or mask these contributors to neurobehavioural functioning, these systems are highly conserved, and relatively resistant to long-term interventions. While several countermeasures, including naps, (in particular prophylactic naps), and pharmacological wake promoting agents, (such as caffeine or modafinil), provide temporary reinforcement of the neurobehavioural system, it remains that the only way to truly reverse the neurobehavioural deficits induced by sleep loss, is to obtain adequate sleep.

## 8. ACKNOWLEDGMENTS

Supported in part by NIH grant NR04281; NASA Cooperative Agreement NCC 9-58 with the National Space Biomedical Research Institute; AFOSR grant F49620-00-1-0266 and The Institute for Experimental Psychiatry Research Foundation.

## 9. REFERENCES

1. Krueger, J. M. & F. Obal Jr.: Sleep function. *Front. Biosci.* 8, d511-d519 (2003)
2. Benington, J. H.: Sleep homeostasis and the function of sleep. *Sleep* 23, 959-966 (2000)
3. Giuditta, A., M. V. Ambrosini, P. Montagnese, P. Mandile, M. Cotugno, G. Grassi Zucconi & S. Vescia: The sequential hypothesis of the function of sleep. *Behav. Brain Res.* 69, 157-166 (1995)
4. Rogers, N. L., M. P. Szuba, J. P. Staab, D. L. Evans & D. F. Dinges: Neuroimmunologic aspects of sleep and sleep loss. *Sem. Clin. Neuropsychiatry* 6, 295-307 (2001)
5. Spiegel, K., R. Leproult & E. Van Cauter: Impact of sleep debt on metabolic and endocrine function. *Lancet* 354, 1435-1439 (1999)
6. Dawson, D., N. Lamond, K. Donkin & K. J. Reid: Quantitative similarity between the cognitive psychomotor performance decrement associated with sustained wakefulness and alcohol intoxication. In: *Managing Fatigue in Transportation*. Eds: L. Hartley, Pergamon, Oxford, 231-255 (1998)
7. Dinges, D. F. & N. B. Kribbs: Performing while sleepy: Effects of experimentally-induced sleepiness. In: *Sleep, Sleepiness and Performance*. Eds: T. H. Monk, John Wiley & Sons Ltd, 97-128 (1991)
8. Dinges, D. F.: Performance effects of fatigue. *NTSB/ NASA Fatigue Symposium*, 41-46 (1995)
9. Moore, R. Y.: Organization and function of a central nervous system circadian oscillator: the suprachiasmatic hypothalamic nucleus. *Fed. Proc.* 42, 2783-2789 (1983)
10. Miller, J. D., L. P. Morin, W. J. Schwartz & R. Y. Moore: New insights into the mammalian circadian clock. *Sleep* 19, 641-667 (1996)
11. Czeisler, C. A. & K. P. Wright Jr: Influence of light on circadian rhythmicity in humans. In: *Regulation of Sleep and Circadian Rhythms*. Eds: F. W. Turek & P. C. Zee, Marcel Dekker, Inc, New York, 149-180 (1999)
12. Borbely, A. A. & P. Achermann: Sleep homeostasis and models of sleep regulation. In: *Principles and Practice of Sleep Medicine*. Eds: M. H. Kryger, T. Roth & W. C. Dement, W. B. Saunders Company, Philadelphia, 377-390 (2000)
13. Folkard, S., P. Totterdell, D. Minors & J. Waterhouse: Dissecting circadian performance rhythms: implications for shiftwork. *Ergonomics* 36, 283-288 (1993)
14. Freivalds, A., D. B. Chaffin & G. D. Langolf: Quantification of human performance circadian rhythms. *Am. Ind. Hygiene Assoc. J.* 44, 643-648 (1983)
15. Gillooly, P. B., M. H. Smolensky, D. L. Albright, B. Hsi & D. R. Thorne: Circadian variation in human performance evaluated by the Walter Reed performance assessment battery. *Chronobiol. Int.* 7, 143-153 (1990)
16. Monk, T. H. & V. C. Leng: Interactions between inter-individual and inter-task differences in the diurnal variation of human performance. *Chronobiol. Int.* 3, 171-177 (1986)
17. Monk, T. H., D. J. Buysse, C. F. Reynolds 3rd, S. L. Berga, D. B. Jarrett, A. E. Begley & D. J. Kupfer: Circadian rhythms in human performance and mood under constant conditions. *J. Sleep Res.* 6, 9-18 (1997)
18. Kleitman, N., T. S. & P. Feiveson: The effect of body temperature on reaction time. *Am. J. Physiol.* 121, 495-501 (1938)
19. Kleitman, N. & D. P. Jackson: Body temperature and performance under different routines. *J. Appl. Physiol.* 3, 309-328 (1950)
20. Johnson, M. P., J. F. Duffy, D. J. Dijk, J. M. Ronda, C. Dyal & C. A. Czeisler: Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *J. Sleep Res.* 1, 24-29 (1992)
21. Wright Jr, K. P., J. T. Hull & C. A. Czeisler: Relationship between alertness, performance and body temperature in humans. *Am. J. Physiol.* 283, R1370-R1377 (2002)
22. Patrick, G. T. & J. A. Gilbert: On the effects of loss of sleep. *Psychol. Rev.* 3, 469-483 (1896)
23. Kleitman, N.: Deprivation of sleep. In: *Sleep and Wakefulness*. Ed: N. Kleitman, 215-229 (1963)
24. Babkoff, H., T. Caspy & M. Mikulincer: Subjective sleepiness ratings: the effects of sleep deprivation, circadian



- rhythmicity and cognitive performance. *Sleep* 14, 534-539 (1991)
25. Glenville, M., R. Broughton, A. M. Wing & R. T. Wilkinson: Effects of sleep deprivation on short duration performance measures compared to the Wilkinson auditory vigilance task. *Sleep* 1, 169-176 (1978)
26. Polzella, D. J.: Effects of sleep deprivation on short-term recognition memory. *J. Exp. Psychol. Hum. Learning Mem.* 104, 194-200 (1975)
27. Elkin, A. J. & D. J. Murray: The effects of sleep loss on short-term recognition memory. *Can. J. Psychol.* 28, 192-198 (1974)
28. Lamond, N. & D. Dawson: Quantifying the performance impairment associated with fatigue. *J. Sleep Res.* 8, 255-262 (1999)
29. Mullaney, D. J., D. F. Kripke, P. A. Fleck & L. C. Johnson: Sleep loss and nap effects on sustained continuous performance. *Psychophysiol.* 20, 643-651 (1983)
30. Harrison, Y. & J. A. Horne: Sleep deprivation affects speech. *Sleep* 20, 871-877 (1997)
31. Lubin, A.: Performance under sleep loss and fatigue. In: *Sleep and Altered States of Consciousness*. Eds: S. S. Kety, E. V. Evarts & H. L. Williams, The Williams & Wilkins Company, New York, 507-513 (1967)
32. Horne, J. A. & A. N. Pettitt: High incentive effects on vigilance performance during 72 hours of total sleep deprivation. *Acta Psychologica (Amst)* 58, 123-139 (1985)
33. Webb, W. B. & H. W. Agnew, Jr.: The effects of a chronic limitation of sleep length. *Psychophysiol.* 11, 265-274 (1974)
34. Blagrove, M., C. Alexander & J. A. Horne: The effects of chronic sleep reduction on the performance of cognitive tasks sensitive to sleep deprivation. *Appl. Cog. Psychol.* 9, 21-40 (1995)
35. Friedmann, J., G. Globus, A. Huntley, D. Mullaney, P. Naitoh & L. Johnson: Performance and mood during and after gradual sleep reduction. *Psychophysiol.* 14, 245-250 (1977)
36. Devoto, A., F. Lucidi, C. Violani & M. Bertini: Effects of different sleep reductions on daytime sleepiness. *Sleep* 22, 336-343 (1999)
37. Carskadon, M. A. & W. C. Dement: Cumulative effects of sleep restriction on daytime sleepiness. *Psychophysiol.* 18, 107-113 (1981)
38. Dinges, D. F., F. Pack, K. Williams, K. A. Gillen, J. W. Powell, G. E. Ott, C. Aptowicz & A. I. Pack: Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep* 20, 267-277 (1997)
39. Brunner, D. P., D. J. Dijk & A. A. Borbely: Repeated partial sleep deprivation progressively changes in EEG during sleep and wakefulness. *Sleep* 16, 100-113 (1993)
40. O'Meara, K. H., N. L. Rogers, I. Powell, J. W., M. M. Carlin, M. P. Szuba & D. F. Dinges: Subjective adaptation during chronic sleep restriction at an adverse circadian phase. *Sleep* 25, A310-A311 (2002)
41. Maislin, G., N. L. Rogers, N. J. Price, J. M. Mullington, M. P. Szuba, H. P. A. van Dongen & D. F. Dinges: Response surface modeling of the effects of chronic sleep restriction with and without diurnal naps. *Sleep* 24, 242-243 (2001)
42. Rogers, N. L., H. P. A. Van Dongen, I. Powell, J. W., M. M. Carlin, M. P. Szuba, G. Maislin & D. F. Dinges: Neurobehavioural functioning during chronic sleep restriction at an adverse circadian phase. *Sleep* 25, A126-A127 (2002)
43. Van Dongen, H. P. A., G. Maislin, J. M. Mullington & D. F. Dinges: The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26, 117-126 (2003)
44. Williams, H. L., A. Lubin & J. J. Goodnow: Impaired performance with acute sleep loss. *Psycholo. Mon. Gen. Appl.* 73, 1-25 (1959)
45. Bills, A. G.: Blocking: A new principle in mental fatigue. *Am. J. Psychol.* 43, 230-245 (1931)
46. Warren, N. & B. Clark: Blocking in mental and motor tasks during a 65-hour vigil. *J. Exp. Psychol.* 21, 97-105 (1937)
47. Bjerner, B.: Alpha depression and lowered pulse rate during delayed actions in a serial reaction test: A study of sleep deprivation. *Aviat. Space Environ. Med.* 6, 233-235 (1949)
48. Broadbent, D. E.: Noise, paced performance and vigilance tasks. *Brit. J. Psychol.* 44, 295-303 (1953)
49. Dinges, D. F. & J. W. Powell: Sleepiness impairs optimum response capability. *Sleep Res.* 18, 366 (1989)
50. Lisper, H. O. & A. Kjellberg: Effects of 24-hour sleep deprivation on rate of decrement in a 10-minute auditory reaction time task. *J. Exp. Psychol.* 96, 287-90 (1972)
51. Doran, S. M., H. P. Van Dongen & D. F. Dinges: Sustained attention performance during sleep deprivation: evidence of state instability. *Arch. Ital. Biol.* 139, 253-267 (2001)
52. Harrison, Y. & J. A. Horne: Sleep loss impairs short and novel language tasks having a prefrontal focus. *J. Sleep Res.* 7, 95-100 (1998)
53. Harrison, Y., J. A. Horne & A. Rothwell: Prefrontal neuropsychological effects of sleep deprivation in young adults--a model for healthy aging? *Sleep* 23, 1067-1073 (2000)
54. Dorrian, J., N. L. Rogers, C. Ryan, M. P. Szuba & D. F. Dinges: Comparing the effects of total sleep deprivation and restricted diurnal sleep on prefrontal neuropsychological functioning. *Sleep* 25, A444 (2002)
55. Dagher, A., A. M. Owen, H. Boecker & D. J. Brooks: Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain* 122, 173-187 (1999)
56. Diwadkar, V. A., P. A. Carpenter & M. A. Just: Collaborative activity between parietal and dorso-lateral prefrontal cortex in dynamic spatial working memory revealed by fMRI. *Neuroimage* 12, 85-99 (2000)
57. Kroger, J. K., F. W. Sabb, C. L. Fales, S. Y. Bookheimer, M. S. Cohen & K. J. Holyoak: Recruitment of anterior dorsolateral prefrontal cortex in human reasoning: a parametric study of relational complexity. *Cerebral Cortex* 12, 477-485 (2002)
58. Mottaghy, F. M., M. Gangitano, R. Sparing, B. J. Krause & A. Pascual-Leone: Segregation of areas related to visual working memory in the prefrontal cortex revealed by rTMS. *Cerebral Cortex* 12, 369-375 (2002)
59. Zysset, S., O. Huber, E. Ferstl & D. Y. von Cramon: The anterior frontomedian cortex and evaluative judgment: an fMRI study. *Neuroimage* 15, 983-991 (2002)
60. Drummond, S. P. & G. G. Brown: The effects of total sleep deprivation on cerebral responses to cognitive performance. *Neuropsychopharm.* 25, S68-S73 (2001)

61. Drummond, S. P., G. G. Brown, J. L. Stricker, R. B. Buxton, E. C. Wong & J. C. Gillin: Sleep deprivation-induced reduction in cortical functional response to serial subtraction. *Neuroreport* 10, 3745-3748 (1999)
62. Thomas, M., H. Sing, G. Belenky, H. Holcomb, H. Mayberg, R. Dannals, H. Wagner, D. Thorne, K. Popp, L. Rowland, A. Welsh, S. Balwinski & D. Redmond: Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *J. Sleep Res.* 9, 335-352 (2000)
63. Drummond, S. P., G. G. Brown, J. C. Gillin, J. L. Stricker, E. C. Wong & R. B. Buxton: Altered brain response to verbal learning following sleep deprivation. *Nature* 403, 655-657 (2000)
64. Baddeley, A.: Working memory. *Science* 255, 556-559 (1992)
65. Baddeley, A. D.: Is working memory still working? *The Am. Psychol.* 56, 851-864 (2001)
66. Engle, R. W.: What is working memory capacity? In: The nature of remembering: Essays in honor of Robert G. Crowder. Eds: H. L. Roediger, J. S. Nairne, I. Neath & A. Suprenant, S., American Psychological Association Press, Washington D. C., 297-314 (2001)
67. Abi-Dargham, A., O. Mawlawi, I. Lombardo, R. Gil, D. Martinez, Y. Huang, D. R. Hwang, J. Keilp, L. Kochan, R. Van Heertum, J. M. Gorman & M. Laruelle: Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J. Neurosci.* 22, 3708-3719 (2002)
68. Cools, R., E. Stefanova, R. A. Barker, T. W. Robbins & A. M. Owen: Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. *Brain* 125, 584-594 (2002)
69. McCarthy, G., A. M. Blamire, A. Puce, A. C. Nobre, G. Bloch, F. Hyder, P. Goldman-Rakic & R. G. Shulman: Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proc. Natl. Acad. Sci. U.S.A.* 91, 8690-8694 (1994)
70. Perlstein, W. M., C. S. Carter, D. C. Noll & J. D. Cohen: Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *Am. J. Psychiatry* 158, 1105-13 (2001)
71. Dinges, D. F., W. G. Whitehouse, E. Carota Orne & M. T. Orne: The benefits of a nap during prolonged work and wakefulness. *Work and Stress* 2, 139-153 (1988)
72. Dinges, D. F., S. M. Doran, J. Mullington, H. P. van Dongen, N. Price, S. Samuel, M. M. Carlin & J. W. Powell: Neurobehavioral effects of 66 hr of sustained low-dose caffeine during 88 hr of total sleep deprivation. *Sleep* 23, A20-A21 (2000)
73. Helmus, T., L. Rosenthal, C. Bishop, T. Roehrs, M. L. Syron & T. Roth: The alerting effects of short and long naps in narcoleptic, sleep deprived, and alert individuals. *Sleep* 20, 251-257 (1997)
74. Naitoh, P.: Circadian cycles and restorative power of naps. In: Biological Rhythms, Sleep and Shift Work. Eds: L. C. Johnson, D. I. Tepas, W. P. Colquhoun & M. J. Colligan, Spectrum, New York, 553-580 (1981)
75. Tietzel, A. & C. L. Lack: The short-term benefits of brief and long naps following nocturnal sleep restriction. *Sleep* 24, 293-300 (2001)
76. Takahashi, M. & H. Arito: Maintenance of alertness and performance by a brief nap after lunch under prior sleep deficit. *Sleep* 23, 812-819 (2000)
77. Gillberg, M.: The effects of two alternative timings of a one-hour nap on early morning performance. *Biol. Psych.* 19, 45-54 (1984)
78. Andersen, C. M., G. Maislin, H. P. A. Van Dongen, N. L. Rogers, J. W. Powell, M. M. Carlin, J. M. Mullington & D. F. Dinges: Effect of chronically reduced nocturnal sleep, with and without daytime naps, on neurobehavioral performance. *Sleep* 23, A74-A75 (2000)
79. Dinges, D. F., M. T. Orne, W. G. Whitehouse & E. C. Orne: Temporal placement of a nap for alertness: contributions of circadian phase and prior wakefulness. *Sleep* 10, 313-329 (1987)
80. Nicholson, A. N., P. A. Pascoe, T. Roehrs, T. Roth, M. B. Spencer, B. M. Stone & F. Zorick: Sustained performance with short evening and morning sleeps. *Aviat. Space Environ. Med.* 56, 105-114 (1985)
81. Bonnet, M. H.: The effect of varying prophylactic naps on performance, alertness and mood throughout a 52-hour continuous operation. *Sleep* 14, 307-315 (1991)
82. Bonnet, M. H. & D. L. Arand: The use of prophylactic naps and caffeine to maintain performance during a continuous operation. *Ergonomics* 37, 1009-1020 (1994)
83. Bonnet, M. H., S. Gomez, O. Wirth & D. L. Arand: The use of caffeine versus prophylactic naps in sustained performance. *Sleep* 18, 97-104 (1995)
84. Gander, P. H., R. C. Graeber, L. J. Connell & K. B. Gregory: Crew factors in flight operations VIII: Factors influencing sleep timing and subjective sleep quality in commercial long-haul flight crews. NASA Ames Research Center, Moffett Field, CA, Technical Memorandum No. 103852, 1-38 (1991)
85. Co, E. L., K. B. Gregory, J. M. Johnson & M. R. Rosekind: Crew factors in flight operations XI: A survey of fatigue factors in regional airline operations. NASA Ames Research Center, Moffett Field, CA, Technical Memorandum No. 1999-208799, 1-43 (1999)
86. Rosekind, M. R., E. L. Co, K. B. Graeber & D. L. Miller: Crew factors in flight operations XIII: A survey of fatigue factors in corporate/executive aviation operations. NASA Ames Research Center, Moffett Field, CA, Technical Memorandum No. 2000-209610, 1-70 (2000)
87. Rosekind, M. R., R. C. Graeber, D. F. Dinges, L. J. Connell, M. S. Rountree, C. L. Spinweber & K. A. Gillen: Crew factors in flight operations IX: Effects of planned cockpit rest on crew performance and alertness in long-haul operations. NASA Ames Research Center, Moffett Field, CA, Technical Memorandum No. 1994-108839, 1-82 (1994)
88. Opstad, P. K., R. Ekanger, M. Nummestad & N. Raabe: Performance, mood, and clinical symptoms in men exposed to prolonged, severe physical work and sleep deprivation. *Aviat. Space Environ. Med.* 49, 1065-1073 (1978)
89. Bugge, J. F., P. K. Opstad & P. M. Magnus: Changes in the circadian rhythm of performance and mood in healthy young men exposed to prolonged, heavy physical work, sleep deprivation, and caloric deficit. *Aviat. Space Environ. Med.* 50, 663-668 (1979)
90. Haslam, D. R.: The military performance of soldiers in continuous operations. Variations in Work-Sleep

## Sleep loss & neurobehavioural function

- Schedules: Effects on Health and Performance, San Diego, 549-580 (1979)
91. Naitoh, P., T. Kelly & H. Babkoff: Sleep inertia: best time not to wake up? *Chronobiol. Int.* 10, 109-118 (1993)
92. Sallinen, M., M. Harma, T. Akerstedt, R. Rosa & O. Lillqvist: Promoting alertness with a short nap during a night shift. *J. Sleep Res.* 7, 240-247 (1998)
93. Jewett, M. E., J. K. Wyatt, A. Ritz-De Cecco, S. B. Khalsa, D. J. Dijk & C. A. Czeisler: Time course of sleep inertia dissipation in human performance and alertness. *J. Sleep Res.* 8, 1-8 (1999)
94. Dinges, D. F., E. C. Orne, F. J. Evans & M. T. Orne: Performance after naps in sleep-conducive and alerting environments. Variations in Work-Sleep Schedules: Effects on Health and Performance, San Diego, 677-692 (1979)
95. Ferrara, M., L. De Gennaro & M. Bertini: The effects of slow-wave sleep (SWS) deprivation and time of night on behavioral performance upon awakening. *Physiol. Behav.* 68, 55-61 (1999)
96. Ferrara, M., L. De Gennaro & M. Bertini: Time-course of sleep inertia upon awakening from nighttime sleep with different sleep homeostasis conditions. *Aviat. Space Environ. Med.* 71, 225-229 (2000)
97. Goodenough, D. R., H. B. Lewis, A. Shapiro, L. Jaret & I. Sleser: Dream report following abrupt awakening from different kinds of sleep. *J. Person. Soc. Psychol.* 2, 170-179 (1965)
98. Okuma, T., K. Majamura, A. Hayashi & M. Fujimori: Psychophysical study on the depth of sleep in normal human subjects. *Electroenceph. Clin. Neurophysiol.* 21, 140-147 (1966)
99. Seminara, J. L. & R. J. Shavelson: Effectiveness of space crew performance subsequent to sudden sleep arousal. *Aerospace Med.* 40, 723-727 (1969)
100. Williams, H. L., H. C. Morlock & J. V. Morlock: Instrumental behavior during sleep. *Psychophysiol.* 2, 208-216 (1966)
101. Scott, J. & F. Snyder: "Critical Reactivity" after abrupt awakenings in relation to EEG stages of sleep. *Psychophysiol.* 4, 370 (1968)
102. Akerstedt, T. & M. Gillberg: Effects of sleep deprivation on memory and sleep latencies in connection with repeated awakenings from sleep. *Psychophysiol.* 16, 49-52 (1979)
103. Stones, M. J.: Memory performance after arousal from different sleep stages. *Brit. J. Psychol.* 68, 177-181 (1977)
104. Tassi, P., A. Nicolas, G. Dewasmes, R. Eschenlauer, J. Ehrhart, P. Salame, A. Muzet & J. P. Libert: Effects of noise on sleep inertia as a function of circadian placement of a one-hour nap. *Percep. Mot. Skills* 75, 291-302 (1992)
105. Carlson, V. R., I. Feinberg & D. R. Goodenough: Perception of the duration of sleep intervals as a function of EEG sleep stage. *Physiol. Psychol.* 6, 497-500 (1978)
106. Balkin, T. J. & P. Badiana: Relationship between sleep inertia and sleepiness: cumulative effects of four nights of sleep disruption/restriction on performance following abrupt nocturnal awakenings. *Biol. Psych.* 27, 245-58 (1988)
107. Fort, A. & J. N. Mills: Influence of sleep, lack of sleep and circadian rhythm on short psychometric tests. In: Aspects of human efficiency. Eds: W. P. Colquhoun, English Universities Press, London, 115-127 (1972)
108. Wilkinson, R. T. & M. Stretton: Performance after awakening at different times of night. *Psychonom. Sci.* 23, 283-285 (1971)
109. Bruck, D. & D. L. Pisani: The effects of sleep inertia on decision-making performance. *J. Sleep Res.* 8, 95-103 (1999)
110. Lavie, P. & B. Weler: Timing of naps: effects on post-nap sleepiness levels. *Electroenceph. Clin. Neurophysiol.* 72, 218-224 (1989)
111. Chugh, D. K., T. E. Weaver & D. F. Dinges: Neurobehavioral consequences of arousals. *Sleep* 19, S198-S201 (1996)
112. Achermann, P., E. Werth, D. J. Dijk & A. A. Borbely: Time course of sleep inertia after nighttime and daytime sleep episodes. *Arch. Ital. Biol.* 134, 109-19 (1995)
113. Heslegrave, R. J. & R. G. Angus: The effects of task duration and work-session location on performance degradation induced by sleep loss and sustained cognitive work. *Behav. Res. Meth. Inst. Comp.* 17, 592-603 (1985)
114. Pigeau, R., P. Naitoh, A. Buguet, C. McCann, J. Baranski, M. Taylor, M. Thompson & I. Mack: Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. *J. Sleep Res.* 4, 212-228 (1995)
115. Horne, J. A. & L. A. Reyner: Counteracting driver sleepiness: effects of napping, caffeine, and placebo. *Psychophysiol.* 33, 306-309 (1996)
116. Reyner, L. A. & J. A. Horne: Suppression of sleepiness in drivers: combination of caffeine with a short nap. *Psychophysiol.* 34, 721-725 (1997)
117. Neri, D. F., R. L. Oyung, L. M. Colletti, M. M. Mallis, P. Y. Tam & D. F. Dinges: Controlled breaks as a fatigue countermeasure on the flight deck. *Aviat. Space Environ. Med.* 73, 654-664 (2002)
118. Caldwell, J. A., J. L. Caldwell, J. S. Crowley & H. D. Jones: Sustaining helicopter pilot performance with Dexedrine during periods of sleep deprivation. *Aviat. Space Environ. Med.* 66, 930-937 (1995)
119. Caldwell, J. A., J. L. Caldwell, N. K. Smythe 3rd & K. K. Hall: A double-blind, placebo-controlled investigation of the efficacy of modafinil for sustaining the alertness and performance of aviators: a helicopter simulator study. *Psychopharm.* 150, 272-82 (2000)
120. Magill, R. A., W. F. Waters, G. A. Bray, D. Ryan, S. Smith, J. Volaufova, N. McNevin, M. Hurry & H. R. Lieberman: Effects of tyrosine, caffeine, phentermine, d-amphetamine and placebo during sleep deprivation: II Effects on cognitive and motor performance decrements. *Sleep* 21, 230 (1998)
121. Keister, M. E. & R. J. McLaughlin: Vigilance performance related to extraversion-introversion and caffeine. *J. Expt. Res. Pers.* 6, 5 (1972)
122. Walsh, J. K., M. J. Muehlbach, T. M. Humm, Q. S. Dickins, J. L. Sugerma & P. K. Schweitzer: Effect of caffeine on physiological sleep tendency and ability to sustain wakefulness at night. *Psychopharm.* 101, 271-273 (1990)
123. Zwyghuizen-Doorenbos, A., T. A. Roehrs, L. Lipschutz, V. Timms & T. Roth: Effects of caffeine on alertness. *Psychopharm.* 100, 36-9 (1990)
124. Sicard, B. A., M. C. Perault, M. Enslin, F. Chauffard, B. Vandel & P. Tachon: The effects of 600 mg of slow

## Sleep loss & neurobehavioural function

- release caffeine on mood and alertness. *Aviat. Space Environ. Med.* 67, 859-62 (1996)
125. Rosenthal, L., T. Roehrs, A. Zwyghuizen-Doorenbos, D. Plath & T. Roth: Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharm.* 4, 103-108 (1991)
126. Lumley, M., T. Roehrs, D. Asker, F. Zorick & T. Roth: Ethanol and caffeine effects on daytime sleepiness/alertness. *Sleep* 10, 306-312 (1987)
127. De Valck, E. & R. Cluydts: Slow-release caffeine as a countermeasure to driver sleepiness induced by partial sleep deprivation. *J. Sleep Res.* 10, 203-209 (2001)
128. Lagarde, D., D. Batejat, B. Sicard, S. Trocherie, D. Chassard, M. Enslin & F. Chauffard: Slow-release caffeine: A new response to the effects of a limited sleep deprivation. *Sleep* 23, 651-661 (2000)
129. Kamimori, G. H., D. M. Penetar, D. B. Headley, D. R. Thorne, R. Otterstetter & G. Belenky: Effect of three caffeine doses on plasma catecholamines and alertness during prolonged wakefulness. *Eur. J. Clin. Pharmacol.* 56, 537-544 (2000)
130. Penetar, D., U. McCann, D. Thorne, G. Kamimori, C. Galinski, H. Sing, M. Thomas & G. Belenky: Caffeine reversal of sleep deprivation effects on alertness and mood. *Psychopharm.* 112, 359-365 (1993)
131. Rogers, N. L., N. J. Price, M. P. Szuba, H. P. Van Dongen & D. F. Dinges: Effect of sustained caffeine on core body temperature during 88 hours of sustained wakefulness. *Sleep* 24, 172-173 (2001)
132. Bonnet, M. H. & D. L. Arand: Impact of naps and caffeine on extended nocturnal performance. *Physiol. Behav.* 56, 103-109 (1994)
133. Lorist, M. M., J. Snel & A. Kok: Influence of caffeine on information processing stages in well rested and fatigued subjects. *Psychopharm.* 113, 411-421 (1994)
134. Bonnet, M. H. & D. L. Arand: Consolidated and distributed nap schedules and performance. *J. Sleep Res.* 4, 71-77 (1995)
135. Van Dongen, H. P. A., N. J. Price, J. M. Mullington, M. P. Szuba, S. C. Kapoor & D. F. Dinges: Caffeine eliminates psychomotor vigilance deficits from sleep inertia. *Sleep* 24, 813-819 (2001)
136. Wright Jr., K. P., P. Badia, B. L. Myers & S. C. Plenzler: Combination of bright light and caffeine as a countermeasure for impaired alertness and performance during extended sleep deprivation. *J. Sleep Res.* 6, 26-35 (1997)
137. Warot, D., E. Corruble, C. Payan, J. S. Weil & A. J. Puech: Subjective effects of modafinil, a new central adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine and placebo. *Eur. Psychiatry* 8, 201-208 (1993)
138. Baranski, J. V., C. Cian, D. Esquivie, R. A. Pigeau & C. Raphael: Modafinil during 64 hr of sleep deprivation: Dose-related effects on fatigue, alertness, and cognitive performance. *Mil. Psych.* 10, 173-193 (1998)
139. Brun, J., G. Chamba, Y. Khalfallah, P. Girard, I. Boissy, H. Bastuji, G. Sassolas & B. Claustrat: Effect of modafinil on plasma melatonin, cortisol and growth hormone rhythms, rectal temperature and performance in healthy subjects during a 36 h sleep deprivation. *J. Sleep Res.* 7, 105-114 (1998)
140. Wassensten, N. J., G. Belenky, M. A. Kautz, D. R. Thorne, R. M. Reichardt & T. J. Balkin: Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. *Psychopharm.* 159, 238-247 (2002)
141. Stivalet, P., D. Esquivie, P. A. Barraud, D. Leiffen & C. Raphael: Effects of modafinil on attentional processes during 60 hours of sleep deprivation. *Hum. Psychopharmacol. Clin. Exp.* 13, 501-507 (1998)
142. Batejat, D. M. & D. P. Lagarde: Naps and modafinil as countermeasures for the effects of sleep deprivation on cognitive performance. *Aviat. Space Environ. Med.* 70, 493-498 (1999)
143. Buguet, A., A. Montmayeur, R. Pigeau & P. Naitoh: Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. II. Effects on two nights of recovery sleep. *J. Sleep Res.* 4, 229-241 (1995)
144. Edgar, D. M. & W. F. Seidel: Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. *J. Pharmacol. Expt. Ther.* 283, 757-769 (1997)
145. Hughes, R. J., H. P. A. Van Dongen, D. F. Dinges, N. L. Rogers, K. P. Wright Jr., D. M. Edgar & C. A. Czeisler: Modafinil improves alertness and performance during simulated night work. *Sleep* 24, A200 (2001)
146. Bard, E. G., C. Sotillo, A. H. Anderson, H. S. Thompson & M. M. Taylor: The DICEM map task corpus: Spontaneous dialogue under sleep deprivation and drug treatment. *Speech Comm.* 20, 71-84 (1996)
147. Baranski, J. V. & R. A. Pigeau: Self-monitoring cognitive performance during sleep deprivation: effects of modafinil, d-amphetamine and placebo. *J. Sleep Res.* 6, 84-91 (1997)

**Key Words:** Waking Neurobehavioural Function, Sleep, Sleep Deprivation, Countermeasures, Review

**Send correspondence to:** Naomi L. Rogers, Ph.D., The University of Pennsylvania School of Medicine, Unit for Experimental Psychiatry, 1020 Blockley Hall, 423 Guardian Drive, Philadelphia, PA, 19104-6021, U.S.A. Tel: 215 898 0474, Fax: 215 573 6410, E-mail: nrogers2@mail.med.upenn.edu