Journal of Scientific Research & Reports
3(18): 2434-2449, 2014; Article no. JSRR.2014.18.006

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Modeling the Homeostatic ‘Process S’ to Assess Sleep Misalignment and Excessive Sleepiness in Shift-Workers

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Authors’ contributions

This work was carried out in collaboration between all authors. There is no conflict of interest to be disclosed. The mathematical and statistical data processing was carried on by author BM. All authors equally contributed to the paper production, read and approved the final manuscript and its revision. Neither this nor a similar manuscript under the same authorship has been published or is being considered for publication or will be published entirely or in part elsewhere in English or any other language. All authors read and approved the final manuscript.

Original Research Article

Received 15th May 2014
Accepted 9th July 2014
Published 30th July 2014

ABSTRACT

Aims: To quantify and model mathematically the effects on the subjects’ sleep-wake cycle, alertness, and performance of the sleep phase shift due to working at times of the day when sleep propensity is high.
Methodologies: Thirty-seven police officers working on a fast counterclockwise schedule, filled for 25 consecutive days a self-administered questionnaire about the previous night sleep, subjective fatigue, sleep attacks, errors. For each subject, the homeostatic process was computed according to the Borbély-Achermann model. Night sleep decreased progressively during the shift schedule, with effects on sleep pressure

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accumulation and the subjective feeling of fatigue increasing exponentially in the first four shifts to decrease during the 60-hrs off-duty.

Results: Sleep proved delayed starting from the schedule beginning, with marked differences between the morning and night shifts in the subgroups of subjects who voluntarily did/did not compensate for the sleep deprivation by morning or afternoon naps. Sleep attacks occurred mainly during the night-shift, while errors were more frequent in the morning- and night- shifts.

Conclusion: The temporal misalignment with the circadian drive of the working schedule is a primary cause of sleep disruption, with excessive sleepiness and predictable negative effects on alertness, attention and performance. The available model may help define schedules compatible with the physiological sleep-wake cycle in various workplaces.

Keywords: Shift-work; sleep; homeostatic process; fatigue; sleepiness; errors; modeling.

HIGHLIGHTS

Shift-work is associated with detrimental effects on health and safety.

The most immediate and impairing effects are on sleepiness and fatigue, with increased risk of critical errors.

The homeostatic processes computed according to a mathematical model describe these effects.

Application may help to better organize shift-work and reduce the risk of errors.

1. INTRODUCTION

Propensity to sleep depends on the interaction between the homeostatic ‘process S’ and a circadian rhythm (process C). Process C follows a 24-hr. cycle independent from sleep and waking, with maxima at night and in the early afternoon and an evening minimum around 7-9 p.m. [1]. Process S (*i.e.* the homeostatic sleep pressure) rises exponentially to saturation during wakefulness to then decline during sleep; prolonged or improperly timed wakefulness favors its accumulation over consecutive days and induces excessive daytime sleepiness [2,3]. Models have been applied to predict the effects of different working patterns on sleep pressure, process C and accuracy in work activities by combining data on working hours, sleep and performance, and the relationship among parameters. Most models focus on characteristics of sleep such as sleep propensity [4-7], a linear combination of homeostatic drive, circadian rhythm, and sleep inertia [7,8], etc. Although over schematic and heuristic in purpose, these models have proven able to predict the levels of fatigue and sleepiness associated with different shift patterns, and can help reinforce decision-making at the organizational level and manage the risks due to fatigue.

In today’s societies, most workers are active in non-standard working schedules [8-11]. Work at night and in shifts is known to be associated with a variety of detrimental effects on health and safety [12-14], the most immediate and possibly impairing of which are on sleep and alertness [15-18]. A shift in work timing during the 24 hrs. usually results in desynchronization of the master circadian pacemaker, and effect that will persist for a variable period of time depending on the shift schedule [19] with disruption of the normal circadian sleep/wake periodicity and REM/non-REM sleep cycle [20-22]. The consequences are reduced sleep quality and duration, excessive sleepiness when at work and insomnia at home, fatigue [23-25] and reduced psychomotor performance at work. Adaptation to a shift-work schedule including night shifts induces homeostatic S accumulation as well as phase changes in the physiological circadian rhythms; these changes depend on schedule rotation (backward/forward) and number of successive nights at work [26]. In addition, night work requires being active when propensity to sleep is high and is therefore associated with sleepiness, fatigue, impaired performance and higher risk of errors or accidents [27-36]. The effects of shift-work on sleep increase over the years and complaints of excessive day sleepiness or sleep disorders correlate with seniority [35,37]. There is limited information and awareness of these risks and their changes during life.

Purpose of this prospective study was to test the applicability on the Borbély and Achermann model of process S [5] to investigate the changes in the sleep-wake cycle and their effects on sleepiness at work in a homogeneous group of policemen in relation to their shift-work schedule.

2. METHODS

2.1 Subjects

Thirty-seven motorized patrolmen of the State Police in Genova (Italy) were enrolled in the study. Mean age was 32±5 yr.; seniority as shift-workers was 10±6 yr. Their schedule includes five fast backward rotating shifts organized as it follows:

- Day 1: Evening shift (from 7 p.m. to midnight);
- Day 2: Afternoon shift (from 1 p.m. to 7 p.m.);
- Day 3: Morning shift (from 7 a.m. to 1 p.m.);
- Day 4: Night shift (from midnight to 7 a.m.);
- Day 5: Rest shift (60 hrs. off duty).

In no case there was any history or clinical evidence of medical or psychiatric disorders, sleep disturbances (including OSAS), habitual use or abuse of neuroactive drugs of any kind. All subjects had worked regularly, without overtime duties, vacation, or diseases of any kind in the 30 days preceding observation. Some of them (n=18, hereafter labeled as N subjects) used to take a short nap prior to their shift in the evening or at night and in this study have been considered separately from those who did not (non-nappers; NN).

2.2 Questionnaire

All subjects were requested to fill a self-administered questionnaire [38] at the end of each shift throughout 5 consecutive 5-days schedules (25 questionnaires per subject). The questionnaire concerned the preceding shift and included four sections:

1. Personal data: age, sex, weight, height, body mass index (BMI), education, marital status, number of children, shift-work seniority, task on duty (Table 1);
2. Sleep in the preceding 24 hours: latency to sleep, awakenings during the night sleep, length of sleep periods during night and day, problems at awakening, feeling of fatigue, uneasiness, tiredness, number of naps, sleep attacks;

3. Subjective effects of shift work on everyday life: smoking and drinking habits, coffees, schedule and time allowed for meals, snacks, subjective feeling of tachycardia, number of errors/accidents, forgetfulness, giddiness;
4. Subjective sleepiness score (Epworth Sleepiness Scale; ESS) [39]: subjective propensity to sleep in eight daily situations (from score 0=no sleepiness to score 3=maximum sleep tendency; normal range: 0-24; pathological cutoff: higher than 10). A trait scale such as the ESS was preferred to state scales in order to evaluate the subjects' overall sleepiness and minimize transient changes due to circadian, fluctuations, shift, or contingent events related or unrelated to work.

Table 1. Summary demographics of the study population

Variable (mean; SD)		**%**
Age, years (32; 5)		100
	27-32 years	54
	33-37 years	46
Length of employment, years (10.0; 6)		100
	4-10 years	57
	11-16 years	43
Education level	Low (middle school)	25
	High (high school, degree)	75
Marital status	Single/singled	63
	Married/coupled	37
Offspring	No	63
	Yes	37
Rank	Officer	100
Origin	Northern Italy	50
	Southern Italy	50
Nap	N	49
Non Nappers	NN	51
BMI	18.5-23	35
	23.1-24.9	65

2.3 Errors and Accidents

Errors (*e.g.* in the use of tools or instruments or of calculus and orthography when filling in the questionnaire, etc.) conceivably due to inaccuracy were added to those reported informally by the volunteers or independently by others, as were accidents of any relevance due to unfitting driving.

2.4 Statistical Analysis

2.4.1 Homeostatic factor S

For each subject, the homeostatic process S was computed according to an established mathematical model [40]. The homeostatic sleep propensity time course derives from the observed temporal dynamics of the EEG slow-wave activity. These dynamics are translated into a mathematical formulation by means of a theoretical process S that decreases exponentially during sleep as a function of sleep length and simulates slow-wave activity. The wake time process S is described mathematically based on the assumption that it accumulates exponentially to saturation with wake length. Process S mathematical formulation requires continuity and is therefore based on a recursive iterative formulation, its value depending only on the preceding sleep-wake behavior:

$S_t = S_{t-1} \cdot \exp[-\Delta t / \tau_d]$ Sleep

$S_t = 1 - (1 - S_{t-1}) \cdot \exp[-\Delta t / \tau_r]$ Wake

τ_d and τ_r are time constants, t and t-1 represent time instants, while Δt is the time step.

The mathematical model describes sleep organization over time as a theoretical Process C characterized in order to comply with the sleep organization in a 24-h cycle and representing the alternation of higher and lower sleep propensity periods. In mathematical terms it is easily expressed by means of a skewed sinusoidal wave obtained with a sin waves series, and C_t values depend only on the specific time t.

Sleep timing and duration depend on the two processes interaction that the model assumes as linear. Accordingly, sleep pressure S_t values vary between two thresholds [39], each one being modulated by a circadian process. If H_m and L_m represent their mean values, the two thresholds oscillate as follows:

$H_t = H_m + C_t$ upper threshold

$L_t = L_m + C_t$ lower threshold

On the basis of a linear interaction between C_t and S_t, sleep is theoretically executed when:

$S_t = H_t \Rightarrow S_t = H_m + C_t$

While wake-up is executed when:

$S_t = L_t \Rightarrow S_t = L_m + Ct$

Fig. 1 exemplifies the simulation of an ideal normal subject sleeping only at night (from 11 p.m. to 7 a.m.; time in abscissa from the beginning of simulation (vertical line indicates midnight); oscillations of S_t between the two thresholds L_t and H_t in ordinate.

In real life, most individuals may remain awake ignoring the upper threshold H_t, or wake up earlier or later than L_t values. Therefore if we consider man as a social being, these two rules are generally ignored and:

$S_t \neq H_t$ sleep onset

$S_t \neq L_t$ awakening

Specifically, humans accumulate homeostatic sleep pressure exponentially during prolonged wakefulness. S_t therefore saturates exceeding the upper threshold H_t. This condition (S_t>H_t) is taken into account by the model, that assumes a “temporary threshold suspension effect” [40]. In Fig. 1 this effect is evident during the 40-hours of sleep deprivation.

We applied a model previously described (for details see [41]) and in this contest we assumed that:

1) S increases during wake as an exponentially saturating function to decrease (also exponentially) during sleep episodes, and
2) The level of S in day 1 is equal to the common threshold that in normal condition induces sleep onset ($S_{t=0} = H_m$).

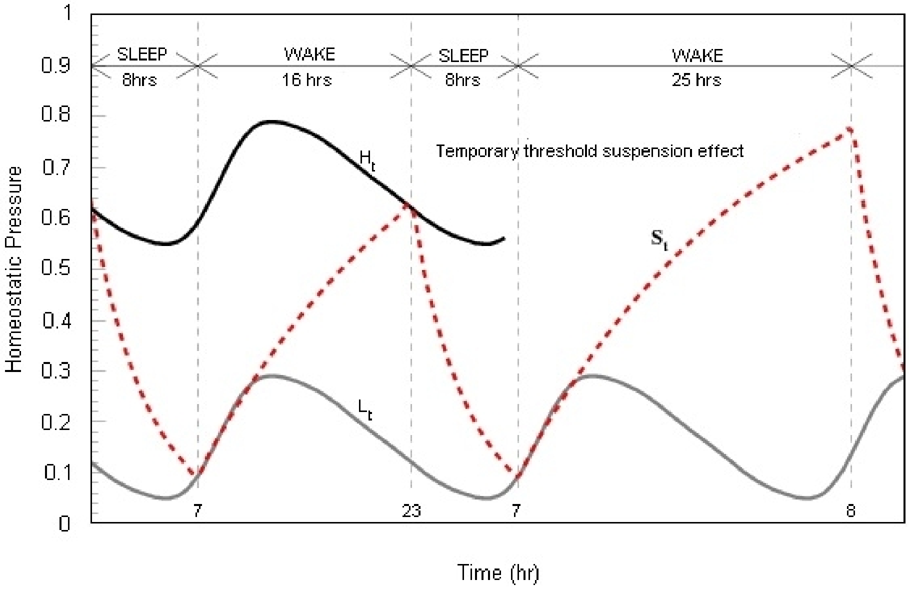

Fig. 1. Modeling of S-levels. Continuous lines represent the thresholds for physiological retiring and awakening according to the two-process model. The dashed line indicates the oscillations in the homeostatic process S. Abscissa: Time from the beginning of the simulation (in hours); ordinate: homeostatic process S. Vertical lines represent the midnight. The retiring threshold is interrupted during the 40-hr. prolonged wakefulness

Subjects taking (N) or not taking naps (NN) during the day were sorted and treated separately. The mean sleep duration and the number and duration of naps were computed for both groups and entered into the simulation of process S accumulation in N (S_N) and NN (S_{NN}) subjects within a schedule. The accumulation of homeostatic sleep pressure related to schedule was estimated by comparing S_N and S_{NN} distributions across the five working shifts by means of the Kolmogorov-Smirnov test. The deviation of S_N and S_{NN} from S-levels reached by an ideal subject attending a regular sleep/wake cycle was described in the two-process model of sleep regulation by the Kolmogorov-Smirnov test. This test was selected as it allows the comparison of continuous distributions, such as S_N and S_{NN}. The temporary H_t threshold suspension effect was studied in both N and NN group.

2.4.2 Subjective fatigue

Feelings of fatigue, uneasiness and tiredness were evaluated every day according to a scale ranging from 0 (absence) to 10 (maximum). Scores were normalized for each subject across the 5-day schedule under the assumption that these estimates reflected the same C-process condition at the time when the questionnaire was filled in (7 p.m.). Previous work shifts are known to affect the impact of a single shift on subjective fatigue [42]. Accordingly, the fatigue trend (*i.e*. the three variables positively correlated) within each schedule was identified by nonlinear regression, with time from beginning of schedule serving as the only independent variable.

2.4.3 Questionnaire and errors

Statistical analysis was exploratory [43,44], with $p<0.005$ threshold for null hypothesis rejection in multiple tests. The five consecutive 5-day schedules of each subject were averaged to reduce statistical fluctuations.

3. RESULTS

3.1 Sleep, Daytime Sleepiness and Process S

Subjects slept at night 7-8 hrs. in average before the evening or afternoon shifts and only 4-5 hr. before the night and morning shifts. The sleep loss was (in part) compensated for by naps taken spontaneously by about 2/3 of subjects in the 11-hrs. interval between morning and night shifts (naps were in early afternoon [48%; duration: 183±67 min.] or early evening [18%; duration: 142±66 min.]). However, only few subjects took naps before the evening shifts (17%; duration: 66±31 min.) and none before the afternoon shifts. Total sleep time during the first day off-duty after the night-shift was limited (about 4 hr.) to then resume to normal (about 8 hr.) the following night; naps during the rest period were occasional (8%; duration: 101±37 min.) (Table 2). Sleep latency and number of awakenings during the night sleep did not differ over the 5-day schedule.

Table 2. Sleep quantity, incidence/duration of naps, and S-levels in each shift of the working schedule

	Evening	Afternoon	Morning	Night	Rest
Sleep length (hours)	8±1	7±1*	5±1*	4±1*	8±1
Subjects taking naps	17%	0%	66%	9%	8%
Nap length (min.)	66±31	----	188±75*	60±103*	101±37
Mean S_{NN}	0.52±0.04*	0.36±0.07	0.30±0.08	0.74±0.03*	0.39±0.18
Mean S_N	0.44±0.05	0.35±0.07	0.30±0.08	0.54±0.05*	0.32±0.16

Mean and standard deviation across subjects.
* *$p<0.005$, comparison with day of rest by Kolmogorov-Smirnov test*

Simulated homeostatic process S within a complete schedule is shown in Fig. 2 for either N (top) and NN (bottom) subjects, together with the theoretical S oscillations between the two thresholds L_t and H_t. The sleep phase was delayed throughout the entire schedule starting from its beginning, with differences between the morning and night shifts. Both S_N and S_{NN} differed from the reference values (Kolmogorov-Smirnov test, $p<0.001$). Moreover, S_N was lower than S_{NN} throughout the schedule (Kolmogorov-Smirnov test, $p<0.001$), with major deviations during the night shift. Notably, the process S increasing throughout the 5-day schedule was compensated for (in part) in the subjects taking naps regularly, but not in those who took naps irregularly or never. As a result, process S crossed significantly the upper threshold only at the end of schedule in subjects taking naps and every day in those taking no naps.

The subjective sleepiness scores ranged from 0 to 15 (6.3±3.3), with six subjects (16%) reporting sleepiness scores above the cutoff (greater than 10), usually regarded as pathological.

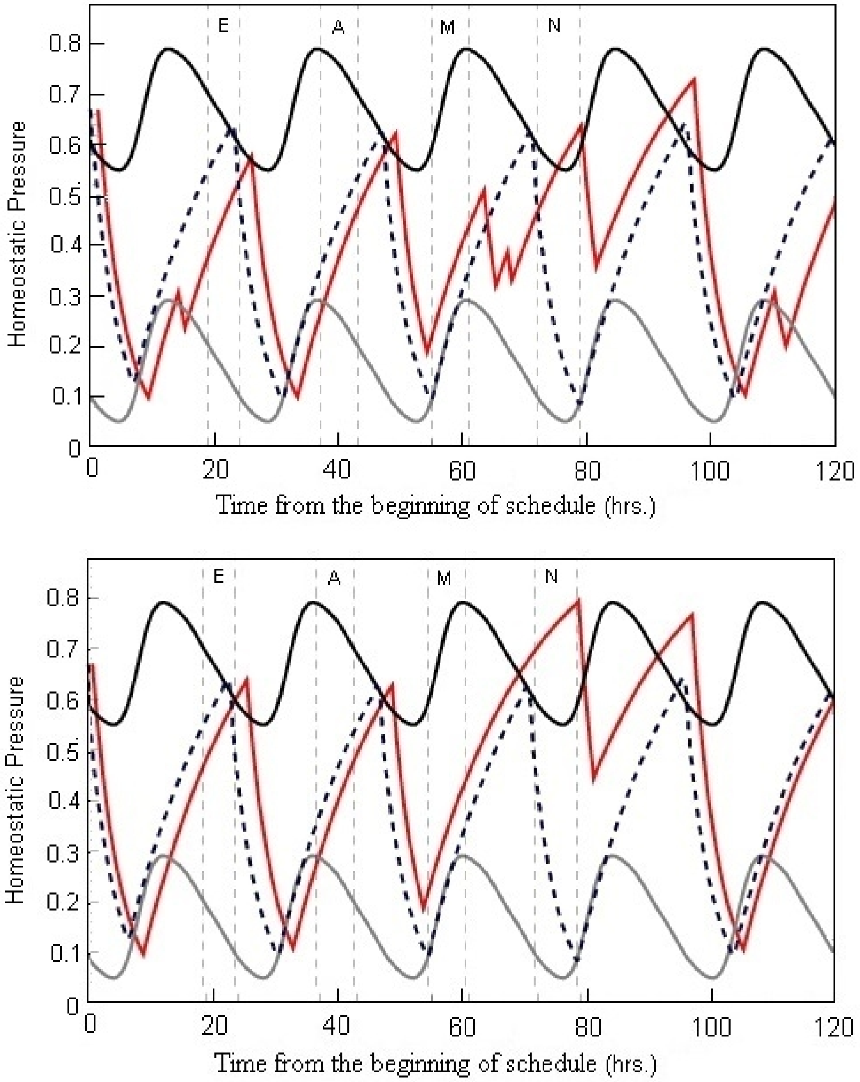

Fig. 2. Modeling of S-levels in the two subgroups of subjects spontaneously taking (top) or not taking naps (bottom).Note the accumulation of process S. The effect is reduced in subjects taking naps

3.2 Subjective Fatigue

Subjective fatigue, uneasiness and tiredness increased during the working days of the schedule and decreased during the 60-hr. rest (Table 3). When normalized and represented as a function of time during the 5-day schedule, fatigue increased exponentially.

Table 3. Subjective feeling of fatigue, of uneasiness and on tiredness in each shift of the working schedule

	Evening	Afternoon	Morning	Night	Rest
Fatigue	2.8±2.3*	4.0±2.8	5.0±2.9*	6.1±2.9*	4.0±2.5
Uneasiness	2.8±2.5	3.3±2.4	4.3±2.7*	5.1±3.1*	2.9±2.3
Tiredness	3.0±2.4	3.7±2.6*	5.1±2.9*	5.2±3.0*	2.9±2.4

Mean and standard deviation across subjects.

** p<0.005, comparison with day of rest by Kolmogorov-Smirnov test*

$$\text{Fatigue}_{\text{UP}} = 0.12\, e^{0.0241\,T}$$

(where T is time from the start of schedule; $R^2=0.60$) from the Shift 1 ('evening') to Shift 4 ('night') to then decrease exponentially from Shift 4 to Shift 1 of the following 5-day schedule

$$\text{Fatigue}_{\text{DOWN}} = 9.25\, e^{-0.0238\,T} - 0.015$$

($R^2=0.61$; Fig. 3). Fatigue did not reset to its initial values during rest time and its levels in the first shift of the following roster were significantly higher than the ones of the previous roster's evening (chi^2 test $p<0.005$).

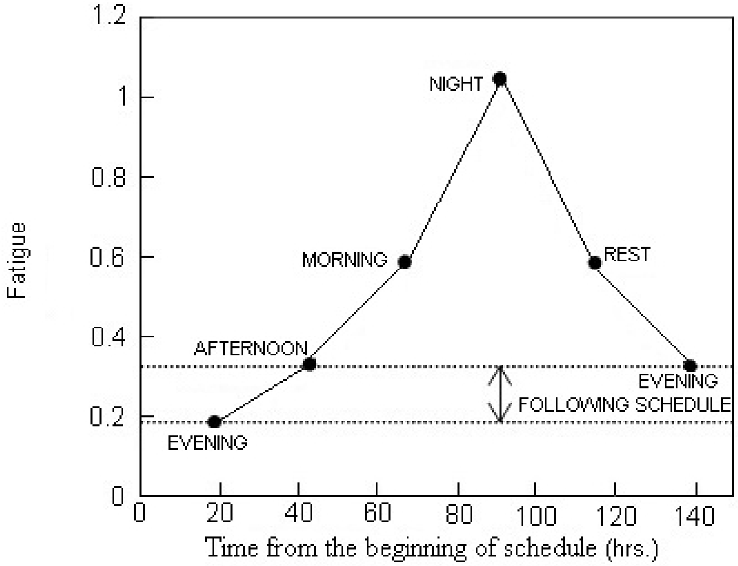

Fig. 3. Fatigue trend in a complete 5-days working schedule: note that fatigue does not reset to initial values in a complete rotating shift system

Smoking did not change throughout the schedule, while the use of coffee was higher during the night shifts (possibly due to fatigue accumulated during the day rather than on work at night) (Kolmogorov-Smirnov test, p<0.005).

3.3 Sleep Attacks and Errors/Accidents

The number of reported sleep attacks while on duty was higher during the night (midnight to 7 a.m.) and morning (7 am to 1 pm) shifts than in the preceding and following shifts

(Kolmogorov-Smirnov test; p<0.0001). Both the reported and observed errors were more frequent during the night shifts, with a mean number of errors higher than one/person/shift (p<0.0001) (Fig. 4); five minor to moderate road accidents due to unfitting driving were reported, all occurring during the night shift.

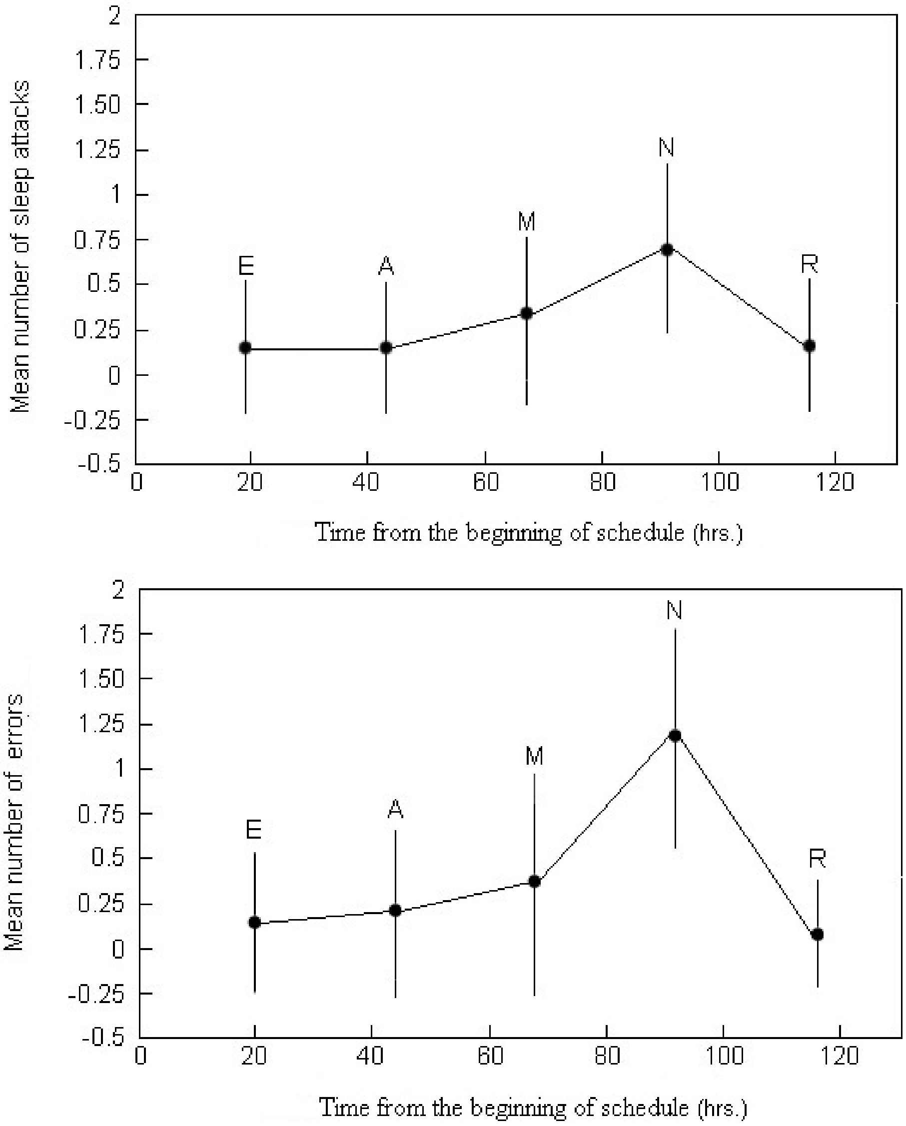

Fig. 4. Sleep attacks (top) and errors (bottom): mean values and standard errors within a complete shift schedule. E=evening; A=afternoon; M=morning; N=night; R= rest

4. DISCUSSION

Ambiguities in the definition of fatigue often result in using fatigue and sleepiness as synonymous [45] to describe relationships with prolonged working and shift work, impaired cognitive performance, reduced safety, or increased risk of lifestyle-related disorders [46]. To help minimize these ambiguities, mathematical models have been implemented, in which fatigue is inferred by analyzing work patterns and circadian events to estimate sleep and wake behaviors. Among these, the three-process model of alertness and the Prior sleep-wake model are currently in use [47,48]. The former is an extension of the two-process model by Borbely & Achermann [5], with the addition of sleep inertia; the latter is relatively simpler and allows process descriptors of fatigue in real time, but minimizes the effects of chronic sleep restriction. Both models are based on averaged data, thus limiting prediction for the individual [49]. Comparison among different models in the treatment of real data is advisable, notably in cohort studies on large databases of physiological data. However, the two-process model by Borbely and Acherman [5] remains applicable, particularly in the theoretical computation of subjective data pertaining the process C and process S ongoing trends; it is also deemed suitable of application in a broad range of conditions to investigate sleep patterns/cycles by either physiological measures or self-assessment [40]. The relationship between work-related fatigue and the risk threshold is known [50], but there is relatively scarce evidence on how models can be applied in workplace settings. In this study, we document applicability of a model based on the original two-process model [5] in investigating fatigue in a real workplace and on data derived from a simple questionnaire rather than from physiological measures. Specifically, data from questionnaire proved usable to model inference about complex homeostatic processes like sleep and the sleep/wakefulness cycle and the model appears to equate a one-step model and as such has a significant level of testing and validation [45].

The process S descriptor of the wakefulness/sleep cycle was found to increase steadily in our subjects' group as a result of the adaptation to the 5-day shift-working schedule, with a progressive circadian delay in the absence of a significant influence by Process C. The 11-hrs. rest between the morning and night shifts did not compensate for the higher S-levels in early morning due to the progressive reduction of night sleep from afternoon to night shifts (with minimum sleep when subjects worked at night or woke up unusually early, *i.e.* between 4.30 am and 6.30 am to attend the morning shift), nor did the 60 hr. interval between the 5-day schedules allow full recovery and a return to baseline values. The high homeostatic pressure described by Process S was compensated for, in part, only by the naps taken voluntarily. This finding is consistent with previous data obtained from a large subjects' sample during a 6 yrs. period of observation showing that napping before night shifts is an effective countermeasure to deterioration of alertness and performance associated with night work, also efficient in preventing the occurrence of accidents [38].

The model also suggests fatigue to have increased during the 5-day schedule, in association with impaired alertness and attention. Night shifts induced a reduction of the sleep duration in the following night, when subjects could not sleep satisfactorily because in opposition to the physiological circadian rhythms or due to familiar or social commitments. As a result, subjective fatigue, tiredness, and sleepiness were frequently reported while on duty. All subjects made at least one error during the morning and night shifts, when the physiological propensity to sleep and Process S were higher, although no shift of the 5-day schedule seems to have been free of errors or sleep attacks. Fatigue associated with working conditions has been identified as a major occupational health and safety risk in most developed countries, with evidence of an association of increasing fatigue with impaired cognitive function [51-53] and performance [52,54-56], increasing error rates and reduced safety [57-59]. Working at night is known to be associated with higher risk [60], including automobile [61], truck [62], and train accidents [63]; our observation is in line with evidence that driving errors resulting in car accidents are more frequent in the early morning and night shifts [64,65]. Today, the cumulative effects of fatigue across shift schedules remain poorly understood [66], while measurements of catecholamine and cortisol excretion in long-distance bus drivers document late recovery [67]. In general, shift-workers report they need rest more often than those who work during the day and their complaint is commonly understood as an effect of sleep deprivation [68,69]. On the contrary, this study further documents that the temporal misalignment of the 5-day working schedule with circadian physiological processes is a primary cause of sleep disruption, with excessive sleepiness and predictable negative effects on sleep, alertness and attention, and performance also in absence of major sleep disturbances such as OSAS [70-72]. The size of the subjects' sample and the use of a questionnaire are limits in this study. Cohort studies on larger samples, possibly with physiological measures supporting the use of questionnaire, are mandatory. Our observations nevertheless further suggest that subjects following a fast backward schedule may never fully adjust their biological rhythms within a single schedule.

Countermeasures promoting sleep, possibly by favoring forward rotating schedules, may help compensate for increased sleepiness and improve sleep, but comprehensive strategies against all negative effects of shift work schedules on human physiology and behavior are still lacking. Sleepiness and insomnia remains crucial effects and further research is necessary to classify individuals particularly vulnerable. Further research is mandatory to investigate the mechanisms regulating the homeostatic factors and fatigue building up within one schedule rotation and determining sleep and fatigue levels in the following shift. In this perspective, the available two-process model by Borbely and Achermann [5] remains fully applicable and reliable in research on shift-workers and may help define possible working schedules compatible with and better suiting the physiological wakefulness-sleep cycle.

5. CONCLUSION

The temporal misalignment of the working schedule with the circadian drive results in sleep disruption, which in turn is a primary cause of negative effects on alertness, attention and performance in shift-workers. Excessive sleepiness and fatigue have been modeled in this study by using the Borbely and Achermann's procedure. This model has proven applicable to predict the effects of shift-working. It would conceivably be instrumental in the investigation of the homeostatic processes and – if systematically applied – would help define schedules compatible with the physiological sleep-wake cycle in various workplaces and able to both reduce the risk of errors and control long-term detrimental effects on health.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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