

Scheduling of sleep/darkness affects the circadian phase of night shift workers

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Abstract

Shift work results in a misalignment between circadian timing and the sleep/wake schedule, leading to irregular and poor quality sleep. Inconsistent input from the daily light cycle further interferes with circadian entrainment. It has been hypothesized that scheduling the sleep/dark cycle on the night shift could aid in promoting adaptation to night shift work by facilitating appropriate phase shifts. In a simulated shift-work study, we compared the ability of two sleep/dark schedules to shift circadian phase. Our results indicate that scheduled sleep/darkness can aid in adaptation to night shift work by inducing both advance and delay phase shifts, depending on the timing of the sleep schedule, although the size of the phase shifts are not sufficient to produce complete adaptation to the night shift. These results have applications to night shift workers, particularly in occupations in which alterations in the timing of light exposure cannot be achieved during working hours.

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The need for 24-h availability of essential services in modern society requires many in the work force to reverse their normal diurnal sleep/wake schedule. About 15 million workers in the US are on non-standard work shifts, including at least 4 million on regular overnight shifts, and an additional 3.5 million on rotating shifts [23]. Many of these workers (e.g., airline pilots, air traffic controllers, nuclear power plant workers, doctors, nurses, law-enforcement and other public safety workers) are employed in professions in which peak functioning during the work shift is critical. Unfortunately, night shift work can exact a substantial cost in terms of health and degraded performance. Night shift workers experience a greater risk of gastrointestinal disease [16], cardiovascular disease [14] and cancer [19,20]. They are also highly prone to vehicular accidents, and experience a higher rate of injuries, industrial accidents, and quality-control errors on the

job than day shift workers [1,22]. Given the prevalence of night shifts in many professions, it has become critical to design measures that can facilitate a successful transition to a night work schedule.

Many of the performance decrements and the sleep disruption associated with night shift work arise due to a misalignment between the timing of the biological clock and the timing of the altered sleep/wake schedule. When night shift workers attempt to invert their normal sleep/wake schedule, their timing of meals, work, and sleep remain perpetually out of phase with the timing of environmental light, the most powerful synchronizer of the circadian pacemaker, thus preventing successful adaptation to a night work schedule. Moreover, the schedules of night workers are often irregular, changing once or twice per week. Furthermore, people who work on the night shift typically attempt to sleep right after returning from work and awaken in the early afternoon resulting in a prolonged period of wakefulness before the start of the next work shift. Therefore, a night shift worker is awake longer

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before starting work than his/her day shift counterpart and thus suffers from greater homeostatic drive for sleep during the work shift, which can interfere with effective functioning.

Ideally any measure that is adopted to ease the transition to night shift work should optimize appropriate circadian entrainment and minimize homeostatic drive for sleep on night shifts. Over the past two decades, it has been demonstrated that exposure to appropriately timed bright light can facilitate the transition from day to night work by rapidly resetting the human circadian pacemaker [3,7–9,12,18]. The resetting properties of exercise [11] and exogenous melatonin [21] have also been investigated. There is also some evidence that shielding night workers from sunlight on their commute home and/or scheduled daytime sleep can help night shift workers transition to a more appropriate sleep/wake schedule [3,7,12].

The role of scheduled sleep in entraining the human circadian system is unclear. It has been argued that darkness during scheduled sleep episodes may function as a circadian synchronizer and thereby facilitate circadian adaptation to night shift work [6,24]. However, the absence of light during daytime sleep changes the timing and distribution of light exposure across the 24-h day and may consequently act as a photic synchronizer, or sleep itself could act as a non-photoc synchronizer of the circadian system. Regardless of the underlying mechanism, it is clear that scheduling appropriate daytime sleep can facilitate the transition to night shift work.

In a night shift work simulation study, we found that subjects assigned to a fixed sleep schedule and subjects who spontaneously adopted consistent sleep schedules adapted better than those who did not have consistently scheduled sleep [12]. Other studies have shown that delaying or advancing bedtimes result in phase delays or advances of circadian rhythms [6], even in the absence of conscious vision [15]. In animals, circadian rhythms have been shown to advance when the LD cycle is advanced and delay when the LD cycle is delayed [2]. In this study we examined the effect of two fixed sleep schedules in facilitating the transition to night shift work by promoting appropriate shifts of the circadian system.

On one schedule, sleep began 7 h after the night shift and lasted 8 h (14:00–22:00), ending 1 h before the next night shift (Pre-Night Shift Sleep), a relative timing of work and sleep typical of what day shift workers do. The other sleep schedule was designed to be similar to what typical night workers do. The sleep episode began 1 h after the night shift and lasted 8 h (08:00–16:00), ending 7 h before the next night shift (Post-Night Shift Sleep). On the day shifts, the sleep episode began at 22:00 h. Thus, relative to the day shift sleep, the Pre-Night Shift Sleep was advanced by 8 h while the Post-Night Shift Sleep was delayed by 10 h. Given the timing of the two different sleep schedules, we expected that relative to the circadian phase on the day shift, circadian phase on the night shift would be advanced to an earlier hour in subjects on the Pre-Night Shift Sleep schedule but delayed to a later hour in subjects on the Post-Night Shift Sleep schedule [5].

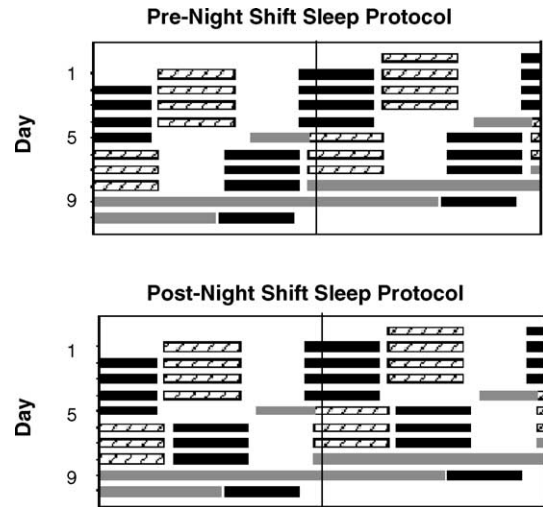


Fig. 1. Double raster plots of the study protocol. *Upper panel:* Schedule followed by Pre-Night Shift Sleep group. *Lower panel:* Schedule followed by Post-Night Shift Sleep group. Hatched bars indicated day and night shifts in the laboratory. Filled bars indicate sleep episodes in the laboratory. Grey bars indicate circadian phase assessments in the laboratory. All other times were spent outside the laboratory. Data are presented in a double raster format, with time of the day across the horizontal axis and the subsequent days of the experiment plotted both to the right of and beneath the previous day.

Eleven men and seven women (26.1 ± 4.8 years) participated in a 10-day simulated shift-work study. All were healthy and free from medical and psychiatric disorders as determined from a screening evaluation, which included a complete physical examination, clinical biomedical tests on blood and urine, electrocardiogram, psychological tests (MMPI and Beck Depression Inventory) and a Sleep Disorders Questionnaire. The protocol was approved by the Human Research Committee of the Partners HealthCare System, and each subject gave written informed consent before starting the study.

The study protocol consisted of 4-day shifts followed by three night shifts (see Fig. 1). Subjects were in the laboratory only during the work shifts and sleep episodes. During the simulated work, subjects performed computer work with breaks every 90 min. Lighting during the work shifts was of typical indoor room illumination and was the same on day shifts and night shifts. To measure the illumination in the laboratory, we placed a light sensor at a height of 137 cm in a horizontal direction at several different positions in the room and averaged the readings. The average illumination in the room was 77.03 ± 33.43 lx ($25 \mu\text{W}/\text{cm}^2$) during the work shifts. The sleep episodes occurred in darkness. During scheduled sleep episodes, subjects were required to remain in bed in the dark. Between the work shifts and sleep episodes, subjects left the laboratory and were free to engage in normal activity. However, they were not allowed to sleep or nap. We ascertained compliance by continuously monitoring activity with a wrist actigraph, also equipped with a light sensor (Actiwatch-L, MiniMitter, Sun River, OR).

On day shifts, the laboratory work shift lasted from 07:00 to 15:00 and the sleep episode from 22:00 to 06:00. Subjects were outside the laboratory from 15:30 to 21:00. The key manipulation in the study design was the timing of the sleep episode (in darkness) and of the resulting exposure to the outside environment during the free time on the night shift schedule. On night shifts, the work shift lasted from 23:00 to 07:00. For the night shift sleep episode, each subject was randomly assigned to one of two schedules: Pre-Night Shift Sleep (14:00–22:00; top panel Fig. 1, $n=9$) or Post-Night Shift Sleep (08:00–16:00; bottom panel Fig. 1, $n=9$). The subjects in the Pre-Night Shift Sleep group were outside the laboratory from 07:30 to 13:00 and subjects in the Post-Night Shift Sleep group from 16:30 to 22:00.

The protocol also included a 6-h constant posture (CP) regimen after the final day shift and a 38-h constant routine (CR) after the final night shift to allow us to assess initial and final phase, respectively, of the endogenous circadian melatonin rhythm [10]. During CP, subjects were seated in dim light (0.91 ± 0.72 lx; $0.41 \mu\text{W}/\text{cm}^2$) from 17:00 to 23:00 and saliva samples (SaliSaver, ALPCO) were collected hourly. During CR, subjects remained awake in a semi-recumbent bed-rest position, in dim light (0.91 ± 0.72 lx; $0.41 \mu\text{W}/\text{cm}^2$) and food was distributed in hourly snacks. Saliva samples were collected hourly and core body temperature was continuously monitored via a rectal thermistor (Yellow Springs Instruments, Yellow Springs, OH).

The Dim Light Salivary Melatonin Onset (DLSMO) was used to assess the phase of the endogenous circadian melatonin rhythm [17]. The saliva samples were assayed for melatonin concentration using a double-antibody radioimmunoassay (assay sensitivity <0.2 pg/ml, precision 8–11%, inter-assay coefficient of variability 8.87% at 1.81 pg/ml and 10.25% at 13.86 pg/ml, intra assay coefficient of variability of 11.1% at 1.6 pg/ml, 11.2% at 17.1 pg/ml; Brigham and Women's Hospital GCRC Core Laboratory). To compute DLSMO, the melatonin data from the CR were fitted with a

3-harmonic model and the level at which saliva concentration reached 25% of the fitted model was calculated. $\text{DLSMO}_{25\%}$ was defined as the time the melatonin levels during CP or CR reached 25% of this fitted maximum. For the CR data, we also computed the midpoint of the melatonin secretion episode and the phase of the endogenous core body temperature rhythm. The midpoint of the melatonin secretion episode was defined as the midpoint between 25% upward and 25% downward crossing points of the melatonin secretion episode. The phase of the endogenous core body temperature rhythm was calculated by fitting a two-harmonic model to the data and the nadir of the fitted temperature model was defined as the phase of the endogenous core body temperature rhythm (CBT_{min}) [4].

Circadian phase, as assessed by dim light salivary melatonin onsets ($\text{DLSMO}_{25\%}$), was not significantly different between the Pre-Night Shift and Post-Night Shift Sleep groups following the day shifts ($20:27 \pm 0:25$ h, $n=8$ versus $21:01 \pm 0:43$ h, $n=9$; $t[15]=2.13$, $p=0.048$; see upper symbols in Fig. 2). One subject from the Pre-Night Shift Sleep group was excluded from this analysis because the data were insufficient to calculate the $\text{DLSMO}_{25\%}$. After three night shifts, $\text{DLSMO}_{25\%}$ in the Pre-Night Shift Sleep group had advanced significantly by 56 ± 28 min (from $20:27 \pm 0:25$ to $19:31 \pm 0:33$ h; $t[7]=1.89$, $p=0.04$; see left panel of Fig. 2). In contrast, $\text{DLSMO}_{25\%}$ in the Post-Night Shift Sleep group had delayed significantly by $2:05 \pm 0:44$ h (from $21:01 \pm 0:40$ to $23:10 \pm 0:53$ h; $t[8]=2.91$, $p=0.009$; see right panel of Fig. 2). This resulted in a significant difference in the $\text{DLSMO}_{25\%}$ of the Pre-Night Shift and Post-Night Shift Sleep groups following the night shifts ($t[15]=2.13$, $p=0.004$; lower symbols in Fig. 2). The circadian phase data were first analyzed using an ANOVA with sleep schedule as a between-subjects factor and shift (day versus night) as within-subjects factor. The ANOVA yielded a significant main effect of sleep schedule (Pre-Night Shift versus Post-Night Shift; $F(1, 15)=6.36$, $p=0.02$) and a significant interaction between *sleep and shift* (day versus night; $F(1, 15)=11.863$,

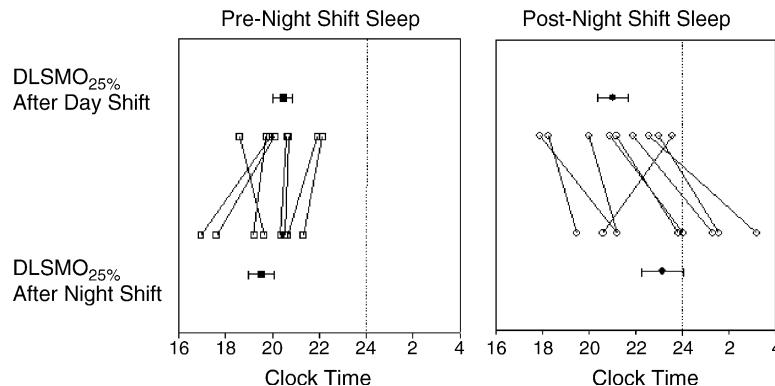


Fig. 2. Individual and average circadian phase following day shifts and night shifts. *Left panel*: Dim light salivary melatonin onset ($\text{DLSMO}_{25\%}$) for subjects in the Pre-Night Shift Sleep group. *Right panel*: $\text{DLSMO}_{25\%}$ for subjects in the Post-Night Shift Sleep group. In both panels, the open symbols represent each subject's individual circadian phase; each subject's phase after the final day shift (upper symbol) is connected to his/her phase after the final night shift (lower symbol). Average data (\pm S.E.) after the day shift and night shift are shown in the filled symbols.

$p = 0.004$) on $DLSMO_{25\%}$. t -Tests were then used to explore this interaction.

Following the night shifts, we examined circadian phase of the melatonin midpoint and the core body temperature nadir (CBT_{min}) in both sleep groups. One subject in the Post-Night Shift Sleep group was excluded from this analysis because the melatonin levels during CR did not reach the 25% downward crossing point and so we were unable to calculate the melatonin midpoint. Both measures of circadian phase occurred at a significantly earlier clock hour in the Pre-Night Shift Sleep group when compared to the Post-Night Shift Sleep group [melatonin midpoint in the Pre-Night Shift Sleep group $01:05 \pm 0:34$ versus Post-Night Shift Sleep group $04:14 \pm 0:56$ ($t[15] = 2.131$, $p = 0.008$; CBT_{min} in the Pre-Night Shift Sleep group $03:38 \pm 0:59$ versus Post-Night Shift Sleep group $06:29 \pm 0:57$; $t[16] = 1.75$, $p = 0.05$]).

We also used data from the light sensor on the wrist actigraph to assess average illumination inside and outside the laboratory in the two groups on the night shifts. Our estimates indicated that average illumination in the laboratory during the night work shifts was not significantly different between the two groups (52.57 ± 13.57 lx versus 44.22 ± 11.33 lx, respectively; $t[10] = 2.23$, $p = 0.64$). During the hours the subjects spent outside the laboratory on the night shift portion of the study, there was no significant difference in the average illumination experienced by subjects in the two groups (381.28 ± 142.4 lx in the Pre-Night Shift Sleep group versus 220.7 ± 90.5 lx in the Post-Night Shift Sleep group; $t[10] = 2.23$, $p = 0.36$). There was also no significant difference between the groups in the amount of time spent in light levels of 200 lx or higher (brighter than that of typical room light) while outside the laboratory, Pre-Night Shift Sleep group 1.58 ± 0.2 h versus Post-Night Shift Sleep group 2.13 ± 0.58 h ($t[10] = 2.31$, $p = 0.41$).

Previous studies using controlled simulations of night shift work have demonstrated the value of applying circadian principles to alleviate problems associated with night shift work [7,8,11,12,18]. The efficacy of timed bright light exposure (during night shift work) in reducing circadian misalignment by inducing appropriate phase shifts is now well known [3,7,9,12]. In the present study, we explored scheduled daytime sleep (in darkness) as an alternative countermeasure to alleviating shift work-induced circadian misalignment: timed sleep/dark and natural light exposure.

Our results showed that the circadian phase of the Pre-Night Shift Sleep group (sleep episode: 14:00–22:00) was advanced by nearly an hour while that of the Post-Night Shift Sleep group (sleep episode: 08:00–14:00) was delayed by more than 2 h. Two independent measures of the phase of the circadian system, salivary melatonin phase and core body temperature phase, were similarly affected, suggesting that the different sleep schedules had shifted the timing of the master circadian pacemaker. Also, the light exposure data from the work shifts and from free time spent outside the laboratory indicate that the average amount of illumination to which subjects were exposed in the two groups was not

significantly different, suggesting that it was the *timing* of the light and dark exposure (achieved as a result of scheduling sleep and time spent outside the laboratory) that influenced the strength and direction of the phase shift.

It has been suggested that scheduled daytime sleep facilitates circadian adaptation to night shift work because darkness itself maybe a circadian synchronizer [6,24]. However, the absence of light during daytime sleep necessarily changes the timing and distribution of light throughout the 24-h day. It is, therefore, not clear whether it was the darkness or the timed exposure to natural light (in the morning for the Pre-Night Shift Sleep group and in the afternoon for the Post-Night Shift Sleep group) that was responsible for the observed phase shifts. It is also possible that sleep itself could have promoted the observed phase shifts by acting as a non-photic synchronizer [15]. From this study it is not possible to judge the relative importance of these factors. Whatever the underlying mechanism, these data indicate that the timing of daytime sleep/darkness and exposure to natural light can contribute to circadian adaptation to night shift work, although alone they are insufficient to produce complete adaptation.

In comparison to the sleep schedule of a day shift worker, the sleep schedule of a typical night shift worker (sleep following work, waking +6 h before the next night shift) results in higher homeostatic sleep pressure during the work shift, magnifying the adverse effects of circadian misalignment on alertness and performance on the job [13]. It seems reasonable to expect that to reduce this problem, a night shift worker would need to adopt a sleep schedule similar to the Pre-Night Shift Sleep of our study, which was designed to minimize homeostatic sleep pressure while facilitating an appropriate phase shift. However, the phase shifts in the study were modest, and consequently the temperature and melatonin phases of the Pre-Night Shift Sleep group, although significantly advanced, still occurred during the night shift. Therefore, despite the reduced homeostatic sleep drive produced by adopting a schedule similar to that in the Pre-Night Shift Sleep group, performance during the night shift on this schedule may still be compromised by circadian misalignment.

To achieve complete adaptation to night shift work one would need to adopt measures, which not only minimize homeostatic sleep pressure but also ensure sufficiently large phase shifts. Thus, it may be necessary to combine scheduled daytime sleep episodes with other appropriately timed countermeasures, such as bright light, melatonin, or exercise, to produce complete adaptation to a night work schedule.

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References

- [1] T. Åkerstedt, C.A. Czeisler, D.F. Dinges, J.A. Horne, Accidents and sleepiness: a consensus statement from the International Conference on Work Hours, Sleep and Accidents, Stockholm, 8–10 September, *J. Sleep Res.* 3 (1994) 195.
- [2] J. Aschoff, K. Hoffmann, H. Pohl, R. Wever, Re-entrainment of circadian rhythms after phase-shifts of the Zeitgeber, *Chronobiologia* 2 (1975) 23–78.
- [3] D.B. Boivin, F.O. James, Circadian adaptation to night-shift work by judicious light and darkness exposure, *J. Biol. Rhythms* 17 (2002) 556–567.
- [4] E.N. Brown, Y. Choe, H. Luithardt, C.A. Czeisler, A statistical model of the human core-temperature circadian rhythm, *Am. J. Physiol. Endocrinol. Metab.* 279 (2000) E669–E683.
- [5] H.J. Burgess, C.I. Eastman, Early versus late bedtimes phase shift the human dim light melatonin rhythm despite a fixed morning lights on time, *Neurosci. Lett.* 356 (2004) 115–118.
- [6] O.M. Buxton, M. L'Hermite-Balériaux, F.W. Turek, E. Van Cauter, Daytime naps in darkness phase shift the human circadian rhythms of melatonin and thyrotropin secretion, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 278 (2000) R373–R382.
- [7] S.J. Crowley, C. Lee, C.Y. Tseng, L.F. Fogg, C.I. Eastman, Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shift work, *J. Biol. Rhythms* 18 (2003) 513–523.
- [8] C.A. Czeisler, The effect of light on the human circadian pacemaker, in: J.M. Waterhouse (Ed.), *Circadian Clocks and Their Adjustment* (Ciba Found. Symp. 183), Chichester, John Wiley and Sons, Inc., 1995, pp. 254–302.
- [9] C.A. Czeisler, M.P. Johnson, J.F. Duffy, E.N. Brown, J.M. Ronda, R.E. Kronauer, Exposure to bright light and darkness to treat physiologic maladaptation to night work, *N. Engl. J. Med.* 322 (1990) 1253–1259.
- [10] J.F. Duffy, D.J. Dijk, Getting through to circadian oscillators: why use constant routines? *J. Biol. Rhythms* 17 (2002) 4–13.
- [11] C.I. Eastman, E.K. Hoese, S.D. Youngstedt, L. Liu, Phase-shifting human circadian rhythms with exercise during the night shift, *Physiol. Behav.* 58 (1995) 1287–1291.
- [12] T.S. Horowitz, B.E. Cade, J.M. Wolfe, C.A. Czeisler, Efficacy of bright light and sleep/darkness scheduling in alleviating circadian maladaptation to night work, *Am. J. Physiol. Endocrinol. Metab.* 281 (2001) E384–E391.
- [13] M.E. Jewett, R.E. Kronauer, Interactive mathematical models of subjective alertness and cognitive throughput in humans, *J. Biol. Rhythms* 14 (1999) 588–597.
- [14] I. Kawachi, G.A. Colditz, M.J. Stampfer, W.C. Willett, J.E. Manson, F.E. Speizer, C.H. Hennekens, Prospective study of shift work and risk of coronary heart disease in women, *Circulation* 92 (1995) 3178–3182.
- [15] E.B. Klerman, D.W. Rimmer, D.J. Dijk, R.E. Kronauer, J.F. Rizzo III, C.A. Czeisler, Nonphotic entrainment of the human circadian pacemaker, *Am. J. Physiol.* 274 (1998) R991–R996.
- [16] A. Knutsson, Health disorders of shift workers, *Occup. Med. (Lond.)* 53 (2003) 103–108.
- [17] A.J. Lewy, R.L. Sack, The dim light melatonin onset as a marker for circadian phase position, *Chronobiol. Int.* 6 (1989) 93–102.
- [18] P.J. Mitchell, E.K. Hoese, L. Liu, L.F. Fogg, C.I. Eastman, Conflicting bright light exposure during night shifts impedes circadian adaptation, *J. Biol. Rhythms* 12 (1997) 5–15.
- [19] E.S. Schernhammer, F. Laden, F.E. Speizer, W.C. Willett, D.J. Hunter, I. Kawachi, G.A. Colditz, Rotating night shifts and risk of breast cancer in women participating in the nurses' health study, *J. Natl. Cancer Inst.* 93 (2001) 1563–1568.
- [20] E.S. Schernhammer, F. Laden, F.E. Speizer, W.C. Willett, D.J. Hunter, I. Kawachi, C.S. Fuchs, Shift work and risk of colorectal cancer in the Nurses' Health Study, *J. Natl. Cancer Inst.* (2003).
- [21] K.M. Sharkey, C.I. Eastman, Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 282 (2002) R454–R463.
- [22] K. Suzuki, T. Ohida, Y. Kaneita, E. Yokoyama, T. Miyake, S. Harano, Y. Yagi, E. Ibuka, A. Kaneko, T. Tsutsui, M. Uchiyama, Mental health status, shift work, and occupational accidents among hospital nurses in Japan, *J. Occup. Health* 46 (2004) 448–454.
- [23] US Department of Labor, Bureau of Labor Statistics, *Workers on Flexible and Shift Schedules in 2001, 2002*, USDL 02-225.
- [24] E. Van Cauter, F.W. Turek, Strategies for resetting the human circadian clock, *N. Engl. J. Med.* 322 (1990) 1306–1308.