Complete or Partial Circadian Re-entrainment Improves Performance, Alertness, and Mood During Night-Shift Work

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Study Objectives: To assess performance, alertness, and mood during the night shift and subsequent daytime sleep in relation to the degree of re-alignment (re-entrainment) of circadian rhythms with a night-work, day-sleep schedule.

Design: Subjects spent 5 consecutive night shifts (11:00 pm-7:00 am) in the lab and slept at home in darkened bedrooms (8:30 am-3:30 pm). Subjects were categorized by the degree of re-entrainment attained after the 5 night shifts. Completely re-entrained: temperature minimum in the second half of daytime sleep; partially re-entrained: temperature minimum in the first half of daytime sleep; not re-entrained: temperature minimum did not delay enough to reach daytime sleep.

Setting: See above.

Participants: Young healthy adults (n = 67) who were not shift workers.

Interventions: Included bright light during the night shifts, sunglasses worn outside, a fixed dark daytime sleep episode, and melatonin. The effects of various combinations of these interventions on circadian re-entrainment were previously reported.[1] Here we report how the degree of re-entrainment affected daytime sleep and measures collected during the night shift.

Measurements and Results: Salivary melatonin was collected every 30 minutes in dim light (<20 lux) before and after the night shifts to determine the dim light melatonin onset, and the temperature minimum was estimated by adding a constant (7 hours) to the dim light melatonin onset. Subjects kept sleep logs, which were verified by actigraphy. The Neurobehavioral Assessment Battery was completed several times during each night shift. Baseline sleep schedules and circadian phase differed among the 3 re-entrainment groups, with later times resulting in more re-entrainment. The Neurobehavioral Assessment Battery showed that performance, sleepiness, and mood were better in the groups that re-entrained compared to the group that did not re-entrain, but there were no significant differences between the partial and complete re-entrainment groups. Subjects slept almost all of the allotted 7 hours during the day, and duration did not significantly differ among the re-entrainment groups.

Conclusions: In young people, complete re-entrainment to the night-shift day-sleep schedule is not necessary to produce substantial benefits in neurobehavioral measures; partial re-entrainment (delaying the temperature minimum into the beginning of daytime sleep) is sufficient. The group that did not re-entrain shows that a reasonable amount of daytime sleep is not enough to produce good neurobehavioral performance during the night shift. Therefore, some re-alignment of circadian rhythms is recommended.

Abbreviations: DLMO, dim light melatonin onset; DSST, digit-symbol substitution test; KSS, Karolinska Sleepiness Scale; LD, light dark; NAB, Neurobehavioral Assessment Battery; POMS, Profile of Mood States; PRC, phase response curve; PRM, probed recall memory task; PVT, psychomotor vigilance task; RT, response time; SSS, Stanford Sleepiness Scale; Tmin, temperature minimum; VAS, visual analog scale

Key Words: night shift work, neurobehavioral tests, performance, sleepiness, circadian rhythms, human, entrainment, melatonin, body temperature, sleep

Citation: Crowley SJ; Lee C; Tseng CY et al. Complete or partial circadian re-entrainment improves performance, alertness, and mood during night-shift work. *SLEEP* 2004;27(6):1077-87.

INTRODUCTION

A GROWING PROPORTION OF THE WORK FORCE OF INDUSTRIALIZED COUNTRIES WORKS NIGHT SHIFTS.[2,3] Sleepiness and performance decrements are most pronounced during the last few hours of the night shift. These impairments can be alleviated somewhat with the use of stimulants such as caffeine[4] and modafinil,[5, 6] but the impairments are not eliminated. Difficulty sleeping during the day can be overcome to some extent with the use of hypnotics, but again the circadian "dip" in alertness and performance during the night shift remains.[7] Furthermore, the use of some stimulants and depressants has negative consequences, such as disrupting sleep, tolerance, dependence, and hangover effects. Melatonin has a small beneficial effect on daytime sleep after the night shift but does not improve sleepiness or performance during the night shift.[8] Theoretically, the best way to produce physiologic adaptation to night work is to phase shift circadian rhythms so that the sleepiest part of the circadian cycle occurs during the daytime sleep period rather than during the night shift, ie, to re-align circadian rhythms with the desired sleep-work schedule.[9,10]

We previously reported the results of a simulated night-shift study that tested 6 combinations of interventions to phase delay circadian rhythms to re-align them with (re-entrain them to) working at night and sleeping during the day.[1] Subjects worked 5 consecutive 8-hour night shifts from 11:00 pm to 7:00 am. To produce a phase delay, all subjects had a 7-hour dark opportunity for sleep starting 1.5 hours after each night shift. Subjects also wore sunglasses with either normal lenses or very dark lenses (15% or 2% transmission) during the commute home. The purpose of the sunglasses was to attenuate sunlight in the morning, which would normally occur during the phase-advance portion of

Disclosure Statement

This is not an industry-sponsored study. Drs. Fogg, Eastman, Crowley, Lee, and Tseng have indicated no financial conflicts of interest.

Submitted for publication February 2004

Accepted for publication April 2004

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the light phase response curve (PRC), and inhibit the desired phase delay.[11] Subjects took a pill, either 1.8-mg sustained-release melatonin or a matching placebo just prior to daytime bedtime at 8:30 am. According to the melatonin PRC of Lewy et al,[12] the use of melatonin at this time should help promote phase delays. Some of the subjects were exposed to intermittent bright light (~5000 lux, 20-minute pulses) during the night shifts in a moving pattern designed to facilitate phase delays.[9] The rest of the subjects remained in ordinary room light (~150 lux) throughout the night.

We found that baseline circadian phase, ie, phase before starting the 5 night shifts, was the most important factor for determining the extent of re-entrainment of circadian rhythms to the sleep and work schedule. We divided our subjects into earlier and later subjects based on whether their baseline dim light melatonin onset (DLMO) occurred before or after midnight, which means that their estimated temperature minima (Tmin) and light PRC crossover points were either before or after the start of the commute home at 7:00 am. (The Tmin occurs about 7 hours after the DLMO.[13-16]) All of the subjects who started with later circadian phases were completely re-entrained regardless of which of the 6 combinations of interventions they were given. Thus, in later subjects, an early, fixed, daytime, sleep-dark episode and normal sunglasses were sufficient to produce complete circadian adaptation to night-shift work. Subjects who started with earlier phases were completely re-entrained when they received bright light during the night shifts (with the exception of 1 out of 12 subjects). The early subjects also benefited from the use of dark sunglasses compared to normal sunglasses. Melatonin did not help to produce larger phase shifts compared to placebo for either early or late subjects. Thus, we recommended intermittent bright light during the night shift, sunglasses on the way home (as dark as possible), and an early fixed time for sleep after the night shift for circadian adaptation to night work. Given the sensitivity of the circadian system to shorter wavelength (blue) light,[17-19] light during the night shift that is enriched with shorter wavelengths and blue-blocker types of sunglasses for the commute home would be best.

Our previous analyses[1] assessed how much the various interventions contributed to the desired phase delay of circadian rhythms and thus to the re-entrainment of circadian rhythms to sleep and work. The purpose of the current analyses was to determine how much this re-entrainment improved performance, sleepiness, and mood during the night shifts and sleep duration during the daytime sleep episodes. These variables were analyzed according to the degree of re-entrainment of circadian rhythms to the night-work day-sleep schedule (not re-entrained, partially re-entrained, and completely re-entrained). In addition, we examined the 24-hour patterns of light exposure.

METHODS

Subjects

Sixty-seven subjects (35 women and 32 men) between the ages of 18 and 43 years (mean age ± SD = 23.9 ± 6.2 years) completed the study. Subjects did not have any obvious medical, psychiatric, or sleep disorders as assessed by interviews, the Minnesota Multiphasic Personality Inventory-2, a sleep questionnaire, and a health questionnaire. Subjects were not taking prescription medications, except for 7 females who were taking oral contraceptives. Individuals who weighed more than 105 kg were excluded so that the fixed dose of melatonin when considered in milligram per kilogram would not vary too much across the sample. Subjects had not worked night shifts or traveled across more than 3 time zones within the month before starting the study. Most subjects had never worked night shifts. The protocol was approved by the Rush University Medical Center Institutional Review Board. All subjects gave written informed consent and were paid for their participation.

Design

The study took place during the summer months (July to September) of 3 consecutive summers. During 7 days of baseline, subjects chose when they slept. The only restriction was that they could not stay awake all night, and during summers 2 and 3 they were told to go to bed before 2:00 am. A standard, fixed sleep schedule was not required because we wanted subjects to display a range of circadian phases at baseline, as is typical of real shift workers. Figure 1 displays days 8 through 14 of the study protocol. Subjects spent the night shifts in the laboratory and slept at home. The daytime dark-sleep episodes occurred on weekdays (Monday through Friday). We made subjects' bedrooms completely dark by covering their windows with thick black plastic on day 3 or 4. We also installed an air conditioner if they did not already have one, as this provided a comfortable sleeping environment. Subjects were told to remain in bed, in the dark, for the entire 7-hour dark-sleep episode (except for necessary bathroom trips), even if they could not sleep.

Subjects recorded bedtime, estimated sleep onset, and estimated wake time (which could have been earlier than out-of-bed time) on daily sleep logs. A separate sleep log was filled out if the

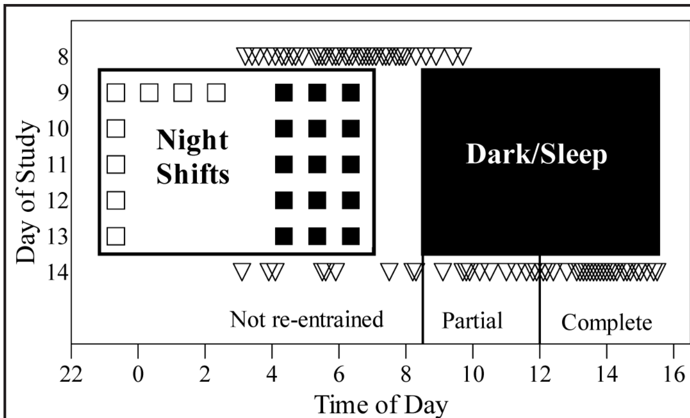

Figure 1—Study protocol after the baseline week. There were 5 simulated night shifts from 11:00 pm to 7:00 am. Subjects went home and remained in completely dark bedrooms from 8:30 am to 3:30 pm. Squares represent the computerized Neurobehavioral Assessment Battery. Open squares: practice test bouts. Closed squares: analyzed test bouts. There was a circadian phase assessment on day 8 (baseline) and day 14 (final). The triangles on these days represent the estimated temperature minima (Tmin) calculated by adding 7 hours to the dim light melatonin onset. Subjects were categorized according to the time of their final Tmin. Not re-entrained: Tmin < 8:30 am, ie, before the previous dark-sleep episode, partial re-entrainment: 8:30 am ≤ Tmin ≤ 12:00, ie, during the first half of the previous dark-sleep episode, and complete re-entrainment: Tmin > 12:00 noon, ie, during the second half of the previous dark-sleep episode.

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subject napped during the baseline week. Napping was not allowed during the second week. They also called the laboratory's voicemail system just prior to bedtime and at wake time. Compliance to the daytime sleep schedule was monitored by an Actiwatch (Actiwatch-64, MiniMitter Inc., Bend, Ore.) worn on the nondominant wrist. Subjects also wore Actiwatches with a photosensor (Actiwatch-L, MiniMitter, Inc.) around their neck like a medallion to monitor their light exposure during the study. This placement captured the light intensity at eye level more accurately than when worn on the wrist. When subjects were in bed, they were told to place the photosensor face up on a nightstand in their bedroom. Every 2 to 3 days, both Actiwatches were downloaded to a computer and checked in the subject's presence (along with sleep logs and phone call records) to ensure that the sleep logs were properly filled in and to verify that subjects were following the dark-sleep restrictions. Four subjects were dropped for noncompliance.

Performance, Sleepiness, and Mood Assessments

During each night shift, subjects completed the Neurobehavioral Assessment Battery (NAB), developed by Dr. David F. Dinges and John W. Powell at the University of Pennsylvania. This computerized battery, which takes about 20 to 25 minutes to complete, was started at 4:05 am, 5:05 am, and 6:05 am during each night shift (see Figure 1). This time of night was chosen because it is typically when real night workers are most sleepy and show the most decrement in performance.[20] Two to three subjects were run simultaneously. Subjects worked on desktop computers under ceiling fixtures with cool white fluorescent lamps dimmed to yield about 25 lux measured at eye level in the angle of gaze. Scores from the 3 test bouts were averaged for each night shift. To minimize learning effects, practice test bouts were completed at 11:05 pm, 0:05 am, 1:05 am, and 2:05 am during the first night shift and at 11:05 pm on subsequent nights (see Figure 1). The following tests were examined: the Psychomotor Vigilance Task (PVT),[21] a Probed Recall Memory Task (PRM),[22] the Digit-Symbol Substitution Test (DSST),[23] the Stanford Sleepiness Scale (SSS),[24] the Karolinska Sleepiness Scale (KSS),[25] 3 visual-analog mood scales (VAS), and the Profile of Mood States (POMS).[26]

The PVT is a simple reaction-time task designed to test sustained attention, vigilance, and speed of response. The PVT ran for 10 minutes during each test bout. Subjects used a hand-held device (13 x 6.5 x 4 cm) with 2 buttons, 1 for the right and 1 for the left hand. Visual reaction time was measured by having subjects press the button controlled by their dominant hand when they saw a series of numbers count up in milliseconds. The counting stopped when the subject pressed the button, and a reaction time was displayed in milliseconds, thus providing feedback each time. Two variables were extracted from this test: mean response time (RT) and average number of lapses per test bout during each night shift. Mean RT included the entire range of RT, including the maximum RT of 30 seconds. If the subject did not respond in 30 seconds, an audio-tone burst alerted the subject. The number of lapses was calculated by first determining the number of RT $\geq$ 500 milliseconds and then transforming that number with the formula, square root (x) + square root (x + 1). This square-root transformation reduced heterogeneity of variance between subjects.[27]

The PRM task displayed a list of 6 word pairs before the PVT for 30 seconds. After the PVT, subjects were presented with 1 word from each pair in a different order and asked to recall the other word in the pair by typing it on the keyboard. Subjects had 5 minutes to recall the matching word. The variable extracted from the PRM task was the number of words recalled.

The DSST presented 9 symbols in a row with associated numbers (1-9) beneath each symbol. The computer program randomly selected 9 out of 24 possible symbols for each test bout. The symbols and numbers remained displayed throughout the test bout. Then, 1 symbol was shown on the screen, and subjects had to type the number associated with that symbol. Immediately after a number was entered, the next symbol was shown. The same symbol was never presented in succession. Following a 15-second practice period, scoring began and continued for 90 seconds. The variable extracted from the DSST was the percentage of correctly paired symbols and numbers.

In each battery of tests, there were 2 presentations of the SSS and VAS, once before and once after the performance-alertness tasks (PVT, PRM, and DSST). The second presentation of both scales is more sensitive than the first, especially at an unfavorable circadian time.[28] Therefore, the second bouts were used in the analysis. The SSS included 7 statements that described feelings of sleepiness ranging from *feeling active and vital*; *alert*; *wide awake* (1) to *almost in reverie*; *sleep onset soon*; *lost struggle to remain awake* (7). The 3 VAS asked "How do you feel right now?" with the scale anchor points: (1) *physically exhausted* to *energetic*, (2) *sharp* to *mentally exhausted*, and (3) *fresh as a daisy* to *tired to death*. The KSS was presented once after the performance or alertness tasks. Subjects were asked to rate their sleepiness on a 9-point scale, ranging from *very alert* (1) to *very sleepy*, *great effort to keep awake, fighting sleep* (9). The POMS was presented at the end of the test bout. Subjects were presented with 65 adjectives and asked to respond to each on a scale ranging from *not at all* (1) to *extremely* (5). Scores of Total Mood Disturbance were analyzed.

Caffeine and Alcohol Restrictions

Subjects documented their daily intake of caffeine, alcohol, and over-the-counter medications. Caffeine was not restricted during the baseline period but was not allowed during the night shifts or after the night shifts in the 1.5 hours before daytime sleep. Alcohol was prohibited 48 hours before the baseline phase assessment until the end of the study. Subjects were administered a Breathalyzer test before each phase assessment and night shift to ensure compliance with this rule. Nonsteroidal anti-inflammatory drugs were prohibited 72 hours before the baseline phase assessment until the end of the study, as these drugs suppress melatonin.[29]

Circadian Phase Assessments

The baseline phase assessment was from 6:30 pm to 3:00 am, after which subjects went to sleep at home. The final phase assessment was from 6:30 pm to 11:00 am. Starting at 7:00 pm, saliva samples were collected every 30 minutes using Salivettes (Sarstedt, Newton, NC). Subjects remained seated in a semirecumbent position in comfortable recliners in dim light (< 20 lux). Caffeine, chocolate, bananas, and lipstick were not allowed 6

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hours before or during each phase assessment, and toothpaste and mouthwash were not allowed during the phase assessments because these products may interfere with the melatonin assay. The use of alcohol and nonsteroidal anti-inflammatory drugs were prohibited as mentioned above. Subjects were allowed to eat and drink except in the 10 minutes before a saliva sample. If subjects ate or drank anything besides water, they were required to brush their teeth with water 10 minutes before the sample while remaining seated. The saliva samples were centrifuged immediately following collection and placed in a freezer. Radioimmunoassay analyses for melatonin were later performed by Pharmasan Labs (Osceola, WI). All samples from a single subject were run in the same assay. The intraassay and interassay variability were 12.1% and 13.2%, respectively. The lower limit of detection of the assay was 0.7 pg/mL.

DATA ANALYSIS

As in our previous study,[1] we categorized the amount of re-entrainment that each subject attained based on the final DLMO. The DLMO was calculated by linearly interpolating between the times of the samples before and after melatonin levels crossed and stayed above a threshold. The threshold for each individual was 35% of the average of the 3 highest melatonin concentrations. To estimate the Tmin, a constant of 7 hours was added to the DLMO because this is the typical temporal relationship (see Introduction). Therefore, those subjects' whose final DLMO was before 1:30 am were defined as not re-entrained because their estimated Tmin occurred before 8:30 am, ie, before daytime sleep. Those subjects' whose final DLMO occurred between 1:30 am and 5:00 am were defined as partially re-entrained because their estimated Tmin occurred during the first half of daytime sleep. Lastly, those subjects' whose final DLMO occurred after 5:00 am were defined as completely re-entrained because their estimated Tmin occurred during the second half of sleep (see Figure 1). Obviously, subjects whose circadian rhythms delayed enough to be classified as partially or completely re-entrained based on their final circadian phase may not have had their Tmin occur during all the daytime sleep periods. However, we can safely assume that subjects categorized as completely re-entrained experienced more days in which their Tmin occurred during daytime sleep than those categorized as partially re-entrained, and those categorized as not re-entrained never had their Tmin during daytime sleep.

Baseline sleep parameters, bedtime, sleep onset, wake time, and sleep duration were calculated from sleep logs kept on nights 1 through 7. The mean of all 7 nights for the baseline sleep variables were calculated for each subject and then averaged for each of the 3 re-entrainment groups. Daytime sleep parameters, sleep onset, wake time, and sleep duration were calculated from sleep logs kept on days 9 through 13 for each subject and averaged for each of the 3 re-entrainment groups. Baseline and daytime sleep durations were defined as the final wake time minus sleep onset minus awakenings within sleep more than 5 minutes in duration.

Two correction factors were applied to the values from the medallion photosensor, one for the error of measurement in the Actiwatch-L and one for wearing sunglasses. If the Actiwatch-L measured more than 10% above or below what was measured by a light meter (Ex-Tech Instruments, Waltham, Mass), then a conversion factor was calculated and applied to the values measured by that Actiwatch-L. The slope of a linear regression line plotted between light levels measured by the Actiwatch-L and the light meter was used as the conversion factor. Then, the light levels were corrected for the type of sunglasses that the subject wore (normal lenses transmit 15% and very dark lenses transmit 2% of light to the eye). Subjects could have been outside during daylight between 7:00 am and 8:30 am and from 3:30 pm until sunset. The correction for sunglasses was applied during these 2 time intervals when light levels were more than 500 lux because we estimated that when the intensity was this high, subjects were outside wearing their sunglasses. Lastly, light levels were averaged into 20-minute bins for each subject and subsequently averaged for the various night-shift light and sunglass-lens conditions.

Performance, sleepiness, and mood measures were analyzed using a 3 × 5 repeated measures analysis of variance with 2 independent factors—re-entrainment group (not re-entrained, partially re-entrained, and completely re-entrained) and night shift (1, 2, 3, 4, and 5). Greenhouse-Geisser corrections were used to correct for violations of sphericity for the within-subjects effects. When a significant interaction was found, simple main-effects analyses were conducted to determine the source of the interaction. Baseline and daytime sleep-log measures were assessed between re-entrainment groups using a one-way analysis of variance. If significant, Tukey HSD posthoc analyses were used to determine which re-entrainment groups were significantly different.

Summary statistics are presented as means and SD unless otherwise indicated.

RESULTS

Twenty-four-Hour Light-Dark Patterns

Figure 2 shows the 4 different patterns of light and dark created by the combinations of interventions implemented during the study. In all of the graphs, light levels were close to or equal to 0 lux from 8:30 am to 3:30 pm when the subjects were required to be in their dark bedrooms trying to sleep. In the top 2 panels, light levels during the night shift did not exceed approximately 150 lux because they were in the room-light condition, whereas in the bottom 2 panels, the bright-light pulses are clearly visible and reach approximately 2500 lux. The sunglasses with darker lenses blocked more light than did those with normal lenses, and this can be seen most clearly by comparing the top 2 panels.

The letters (N, P, and C) in Figure 2, top 2 panels, show (as in our previous analysis[1]) that the amount of re-entrainment attained in the dim light conditions was associated with baseline phase, with later phase producing a greater degree of re-entrainment. In the bright-light conditions, baseline phase was not as important. All but 1 of the subjects given bright light achieved complete re-entrainment regardless of baseline phase. Although the mean baseline Tmin in the completely re-entrained subjects appeared rather late, there was a large range, with some occurring much earlier. The SD for the Tmins of the completely re-entrained subjects in the bottom 2 panels were 0.9 and 1.2 hours, respectively.

Figure 2 also allows us to visualize the time of the crossover point of the light PRC (estimated by the baseline Tmin) in the context of the 24-hour light-dark (LD) pattern. In the top panel, the peak of morning sunlight during the commute home occurred before the Tmin of those completely re-entrained and, thus, dur-

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ing the phase-delay portion of their light PRC. For those not re-entrained and partially re-entrained, the peak of light during the commute home occurred after the Tmin and, thus, on the phase-advance portion of their light PRC. The next panel (dim light + dark sunglasses) shows that the dark sunglasses reduced the light intensity during the commute home to about the same level as during the night shift. Thus, the light during the night shift was as intense as any throughout the day, and it occurred primarily before the Tmin, on the delay portion of the PRC. With bright-light pulses (bottom 2 panels), the light intensity during the rest of the day was relatively much lower. The bright-light pulses occurred primarily before the Tmin, primarily on the delay portion of the light PRC, as per design.

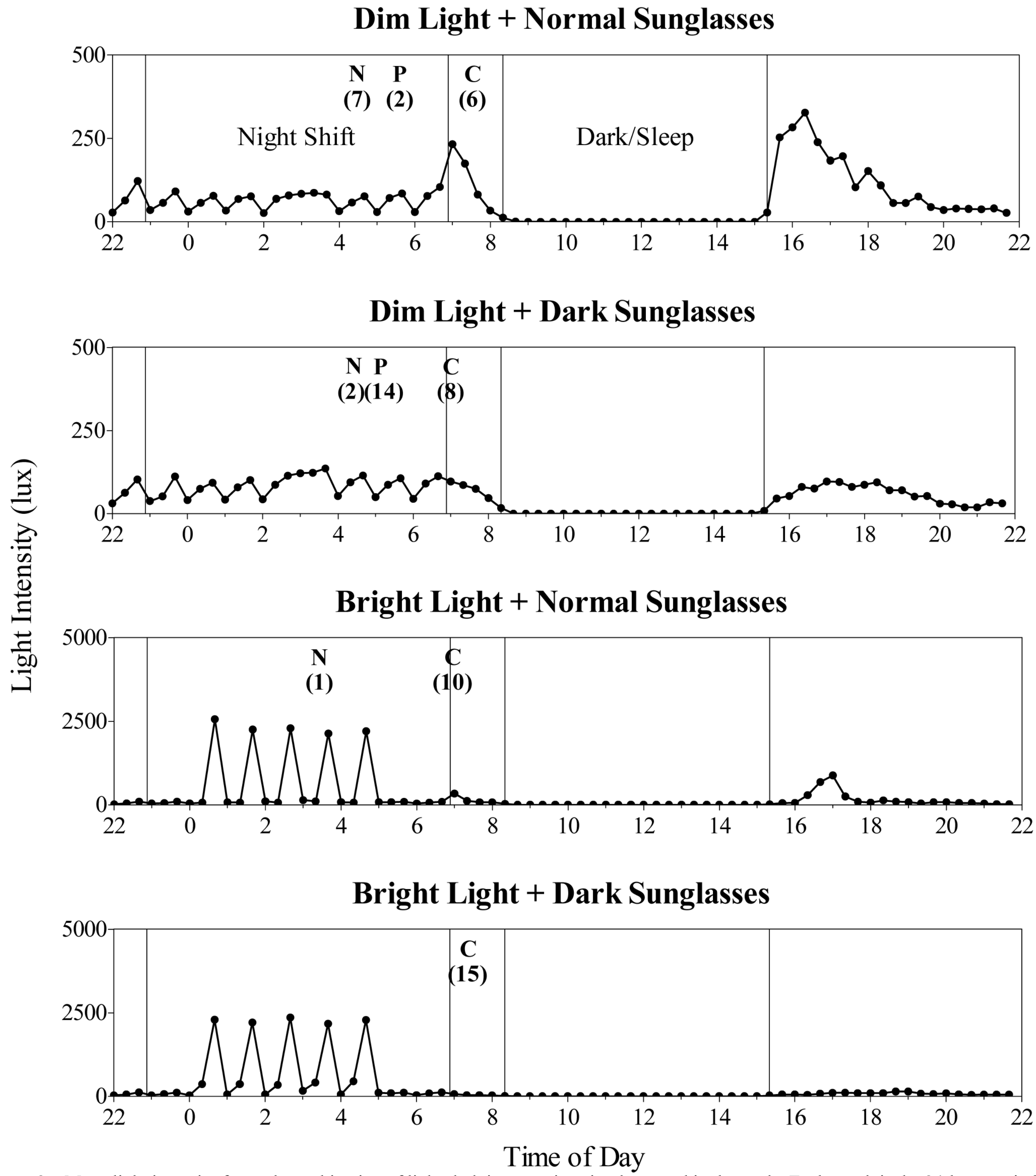

Figure 2—Mean light intensity for each combination of light-dark interventions implemented in the study. Each graph is the 24-hour period including the first night shift and the first dark-sleep episode. Light levels were corrected for Actiwatch error and sunglass-lens transmission (see Methods), then subsequently averaged into 20-minute bins. Vertical lines enclose the points that occurred during the night shift (11:00 pm to 7:00 am) and during dark-sleep (8:30 am to 3:30 pm). Letters at the top of each panel show the mean time of the estimated baseline Tmin for those Not (N), Partially (P), and Completely (C) re-entrained. The number of subjects in each re-entrainment group are in parentheses. Note the different scales on the y-axes.

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Sleep and Circadian Phase

Table 1 shows that the baseline Tmin was later across the 3 re-entrainment groups, again as expected from our previous analysis.[1] The final Tmin was also later, as this was a function of the definition of re-entrainment group by final circadian phase.

Table 1 also shows that the self-selected baseline sleep schedule differed among the 3 re-entrainment groups. The subjects who were subsequently completely re-entrained kept a later baseline sleep schedule than did those who were partially re-entrained, and those who were partially re-entrained kept a later schedule than did those who were not re-entrained. Wake times were at about 10, 9 and 8 am for the 3 groups of subjects. There was also a small difference in baseline sleep duration, with the subjects who were subsequently not re-entrained reporting about 30 minutes less sleep than the subjects in the other 2 groups.

During the night-shift section of the study, all 3 groups reported falling asleep shortly after bedtime at 8:30 am (Table 1). Wake times were slightly later across re-entrainment groups, and daytime sleep duration was slightly longer with more re-entrainment, but there were no statistically significant differences in sleep duration among the 3 re-entrainment groups. However, there was a significant positive correlation between the estimated final Tmin and wake time during the night-shift week ($r = 0.36$, $P = .003$, 2-tailed), and a weak, but significant, correlation between final Tmin and daytime sleep duration ($r = 0.28$, $P = .023$, 2-tailed). As expected, all subjects slept less during the night-shift week, when their sleep opportunity was limited to 7 hours, than during the baseline week, when there was no restriction on sleep length.

Night Shift Performance, Sleepiness, and Mood

Figure 3 displays some of the measures from the computerized batteries during the night shifts. First, the graphs will be described, and then the statistics will be presented. Response time on the PVT (upper-left panel) became longer over the 5 night shifts for the subjects who did not re-entrain. Response time for subjects who attained re-entrainment (either partial or complete) was shorter than for those who did not re-entrain and stayed the same as the 5 night shifts progressed. The number of words recalled in the PRM (upper-right panel) showed a similar trend. Those who did not re-entrain recalled fewer words as the night shifts progressed. Those who attained re-entrainment (partial or complete) recalled more words throughout the 5 night shifts than those who did not re-entrain.

Self-reported sleepiness on the SSS (middle-left panel) showed that the subjects who did not re-entrain became sleepier over the 5 night shifts, while subjects who attained re-entrainment (partial or complete) became less sleepy as the night shifts progressed. The POMS Total Mood Disturbance (middle-right panel) was greater for the subjects who did not re-entrain than for those who attained complete re-entrainment. There was a slight decrease in mood disturbance over the 5 night shifts for those subjects who were partially re-entrained. The Physical Exhaustion VAS (lower-left panel) was greater for those who were not re-entrained. The subjects who attained partial or complete re-entrainment became less physically exhausted as the night shifts progressed. The Mental Exhaustion VAS (lower-right panel) showed a similar trend.

Table 2 shows correlations between final circadian phase and the neurobehavioral measures that were shown in Figure 3. These correlations were significant when the fifth night shift was considered separately (when there was the greatest range in phase

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Table 1—Temperature Minimum Estimated from the Dim Light Melatonin Onset and Sleep Parameters from Sleep Logs

	Degree of Re-entrainment		
	None	Partial	Complete
No.	10	16	41
Age, y	26.9 ± 8.6	25.9 ± 7.3	22.4 ± 4.6
Men, %	50	44	49
Tmin			
Baseline	4:21 am ± 1.0 h	5:12 am ± 0.8 h	7:13 am ± 1.1 h*,†
Final	5:37 am ± 1.9 h	10:53 am ± 0.9 h*	1:48 pm ± 0.8 h*,†
Nighttime sleep, baseline			
Bed time,	11:54 pm ± 1.5 h	00:42 am ± 1.2 h	1:13 am ± 1.0 h*
Sleep onset	0:12 am ± 1.4 h	0:57 am ± 1.1 h	1:41 am ± 1.0 h*, ‡
Wake time	7:55 am ± 1.5 h	9:02 am ± 1.0 h§	9:56 am ± 1.2 h*,†
Duration, h	7.5 ± 0.8	8.0 ± 0.6	8.1 ± 0.7*
Daytime sleep, after night shifts			
Sleep Onset	8:39 am ± 0.3 h	8:40 am ± 0.1 h	8:41 am ± 0.1 h
Wake Time	3:16 pm ± 0.5 h	3:23 pm ± 0.3 h	3:30 pm ± 0.1 h*
Duration, h	6.5 ± 0.6	6.6 ± 0.4	6.7 ± 0.2

Data are presented as mean ± SD. Tmin refers to the time of the temperature minimum estimated from the dim light melatonin onset. For the baseline Tmin in the complete group N=39. Nighttime sleep parameters are the average of days 1 to 7. Daytime sleep parameters are the average of days 9 to 13.
*Significantly different from None group ($P < .05$).
†Significantly different from Partial group ($P < .05$).
‡Trend for difference from Partial group ($P = .063$).
§Trend for difference from None group ($P = .052$).

shifts among subjects), as well as when all 5 night shifts were averaged.

Repeated-measures analyses of variance showed that the main effect of re-entrainment group was significant or close to significance for all of the variables analyzed: mean RT on the PVT [$F_{2,64}$ = 10.97, $P < .001$], lapses on the PVT [$F_{2,64}$ = 9.42, $P < .001$], the percentage correct in the DSST [$F_{2,64}$ = 4.90, $P = .010$], PRM [$F_{2,64}$ = 2.53, $P = .088$], SSS [$F_{2,64}$ = 4.61, $P = .014$], KSS [$F_{2,64}$ = 4.40, $P = .016$], Physical Exhaustion VAS [$F_{2,64}$ = 4.70, $P = .012$], Tiredness VAS [$F_{2,64}$ = 4.14, $P = .020$], Mental Exhaustion VAS [$F_{2,64}$ = 2.62, $P = .080$], and POMS Total Mood Disturbance [$F_{2,64}$ = 2.53, $P = .088$]. There were 2 measures that showed a signifi-

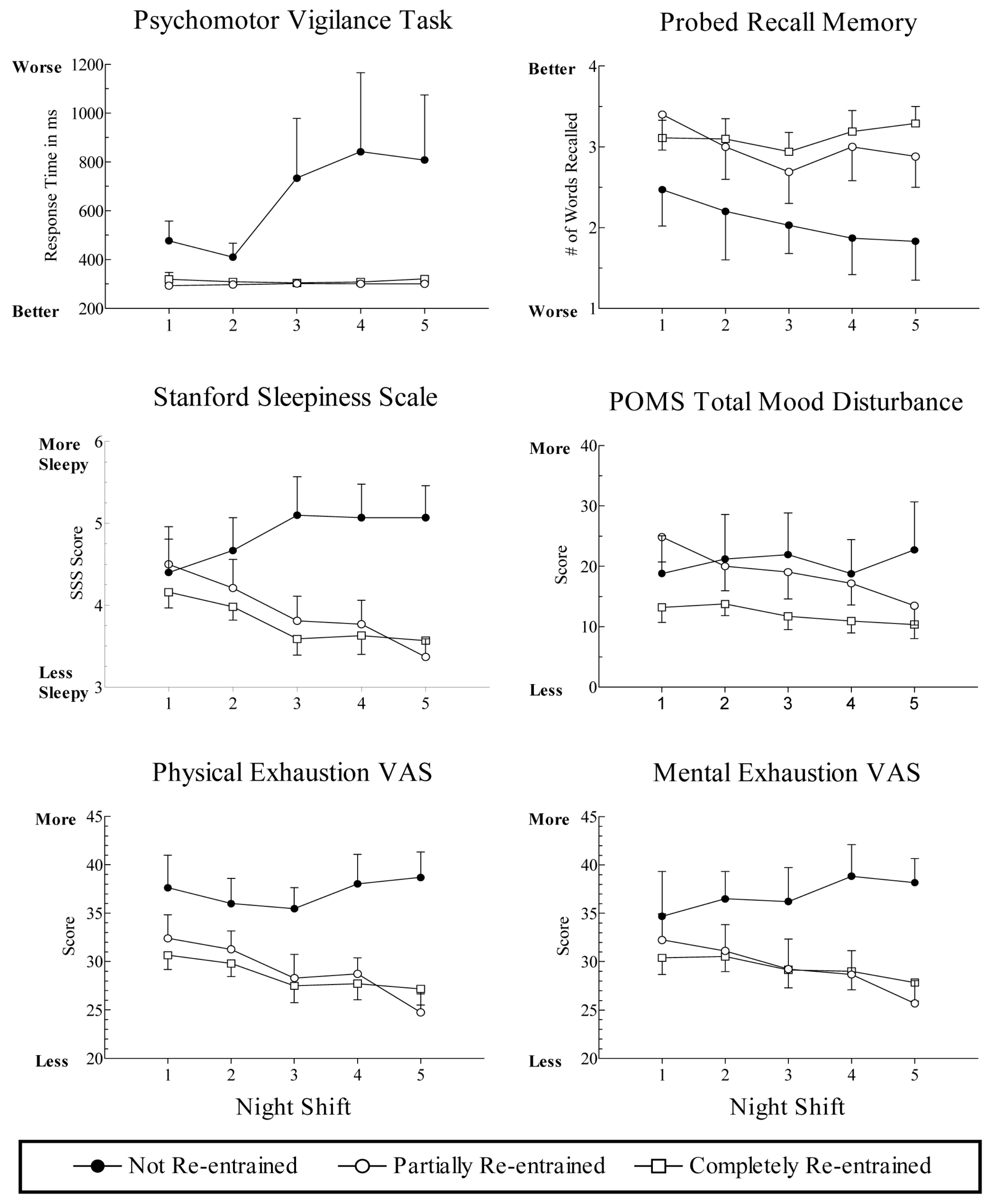

Figure 3—Performance, sleepiness, and mood measures as assessed by the Neurobehavioral Assessment Battery during 5 night shifts. All scores are mean + SEM.

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cant main effect of night shift: mean RT on the PVT [$F_{2,149}$ = 5.63, P = .003] and Physical Exhaustion VAS [$F_{3,221}$ = 2.77, P = .035]. There were also 2 measures that showed a significant interaction: mean RT on the PVT [$F_{5,149}$ = 4.36, P = .001] and SSS [$F_{7,222}$ = 2.56, P = .015]. Simple main-effects analyses revealed that the source of the interactions were significant differences (all P < .001) between the 3 re-entrainment groups during the last 3 night shifts.

DISCUSSION

These data show that performance, alertness, and mood during the night shift were better in the subjects who achieved either partial or complete circadian re-entrainment compared to the subjects who did not re-entrain. However, there were no differences in these neurobehavioral measures between those who were partially and those who were completely re-entrained. In other words, at least for these relatively young subjects, delaying the Tmin into the first half of the daytime sleep period was enough to reap the maximum benefits from re-alignment. Further phase delays, ie, complete re-entrainment, did not yield greater improvements.

There were no differences among the 3 re-entrainment groups in daytime sleep duration. They all slept most of the allotted time. Yet, the groups that re-entrained performed and felt better than the group that did not re-entrain. This confirms previous findings that a reasonable amount of daytime sleep is not enough for optimal night-shift neurobehavioral performance[8] and shows that circadian re-alignment can help mitigate the night-shift decrements.

Twenty-four-Hour Light-Dark Patterns

Given the LD patterns shown in Figure 2, the re-entrainment results can be explained by well-established principles of circadian rhythms: (1) circadian rhythms will phase shift to re-entrain to a shifted LD cycle[30]; (2) the bright-light PRC shows when bright light will facilitate or inhibit re-entrainment[31]; and (3) the circadian system responds to the relative intensities of light throughout the 24-hour day, rather than absolute intensities, to distinguish day from night.[32-34] In all cases, the delay of the sleep-dark episode created a delayed LD cycle, which should produce re-entrainment. However, several subjects did not re-entrain, especially those with earlier baseline phases who were exposed to ordinary dim room light during the night shift and wore normal sunglasses. Those subjects experienced a peak in light exposure during the commute home, which was relatively intense compared to the rest of the 24 hours, and coincided with the phase-advance portion of the PRC (Figure 2, top panel). This further supports our previous study that suggests that most real shift workers do not phase shift because of the morning sunlight during the commute home.[11] A greater proportion of subjects with earlier baseline phases attained at least partial re-entrainment when they wore the dark sunglasses that reduced light levels during the commute home to the levels of the night shift (Figure 2, second panel). There was nothing to prevent their circadian clocks from phase delaying to re-entrain to the delayed LD cycle. Intermittent bright light during the night shift produced complete re-entrainment in all but 1 subject (Figure 2, bottom 2 panels). The most intense light occurred during the night shift, and light levels at other times of day were relatively insignificant, thus producing a strong phase-delay signal to the circadian system. The 1 subject who did not re-entrain had a very early baseline Tmin, but, considering the 24-hour LD pattern, we were surprised that he did not phase delay.

Table 2—Correlations Between Performance, Sleepiness, and Mood During the Night Shifts and the Final Dim-Light Melatonin Onset

Neurobehavioral Measure	Fifth Night Shift	All Night Shifts
PVT, mean response time	-.46****	-.49****
PRM, number of words recalled	+.44***	+.32**
Stanford Sleepiness Scale, score	-.41***	-.39**
POMS, Total Mood Disturbance	-.31*	-.29*
Physical Exhaustion VAS	-.39**	-.39**
Mental Exhaustion VAS	-.39**	-.31*

PVT refers to Psychomotor Vigilance Test; PRM, Probed Recall Memory Task; POMS, Profile of Mood States; VAS, visual analog scale.
*P < .05; **P < .01; ***P < .001; ****P < .0001

These 24-hour LD patterns support the idea that re-entrainment will occur as long as there is a clear delay shift in the dark period and the light during the night shift is more intense than light during the commute home and primarily coincides with the delay portion of the PRC.

Sleep and Circadian Phase

Baseline sleep schedules and baseline phase differed among the 3 re-entrainment groups, with later times resulting in more re-entrainment. This parallels our previous analyses in which subjects were divided into "early" and "late" depending on whether their baseline Tmin occurred before or after the start of the commute time home.[1] Those analyses showed that baseline circadian phase was a major factor contributing to circadian re-entrainment. Thus, an easy suggestion for a night-shift worker could be to delay their sleep schedule for as many days as possible before working a block of night shifts. Obviously, this is impossible with rapidly rotating shift-work schedules that include early-morning shifts. Permanent night-work schedules are thus most conducive to circadian adaptation. In addition, there are individual differences in circadian phase, with "night owls" or "evening-types" naturally having later sleep schedules and later circadian phase positions.[35] It is well known that night-owls adapt better to night work.[36] Our analyses show that this is true not only because of the smaller phase shift required for circadian re-alignment, but also because of the circadian time of light exposure during the commute home.

Daytime sleep durations were slightly longer with more re-entrainment, primarily due to later wake-up times, but the differences in duration among the 3 groups were very small and not statistically significant. When correlations between daytime sleep duration and final circadian phase were calculated, they were statistically significant, showing increased sleep duration with greater re-alignment, but the correlations were very small. In our previous simulated night-shift studies with young subjects, we found larger, moderate, significant correlations between daytime sleep duration and phase shift, showing that circadian re-alignment improved sleep.[11,37,38] Other simulated night-shift studies have also found that phase-delay shifts resulted in better sleep

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quality or duration,[39-41] as did a study of nurses who worked night shifts.[42]

One possible reason for not finding a stronger relationship between sleep duration and circadian re-alignment in the current study is that we limited the time in bed to 7 hours, whereas in the other studies, the daytime dark period was 8 hours. Sleep is most difficult during the day in the last half of the sleep period.[8] Our subjects slept almost all of the allotted 7 hours, and, thus, there may have been a ceiling effect. It is possible that the effect of circadian re-alignment would have been stronger if we had required a longer daytime sleep period. However, we think that most real night-shift workers would not make the time to spend more than about 7 hours in bed during the daytime. Another possible reason that we did not find larger effects is that our subjects were relatively young and therefore more phase tolerant (able to sleep at the wrong circadian phase).[40] Others have found that middle-aged[43] and older people[44] have more difficulty sleeping at an abnormal circadian phase. Thus, re-alignment of circadian rhythms should be more important for preserving sleep in middle-aged and older night workers.

Night-Shift Performance, Sleepiness, and Mood

Even though our subjects slept almost as much as possible during the daytime dark episodes, they had decrements in neurobehavioral measures during the night shift when their circadian rhythms were misaligned. In other words, the subjects who did not re-entrain were sleepier, performed worse, and felt worse than those who achieved re-entrainment. Furthermore, final phase was significantly correlated with improvement in these neurobehavioral measures, showing that greater improvements accompanied greater re-alignment of circadian rhythms. These results are similar to those found in our other simulated night-shift studies in which subjects who had large phase shifts (corresponding to re-entrained subjects) had less POMS fatigue and mood disturbance than did subjects who had small phase shifts (corresponding to not entrained subjects), and there were correlations between the magnitude of the phase shift and POMS scores.[11,37,38] Other simulated night-shift studies used bright light and produced partial re-entrainment[40] or complete re-entrainment[39,41] and also found higher levels of cognitive performance and alertness in the groups that re-entrained compared to control groups that did not.

This study was limited in that baseline (daytime) neurobehavioral measures were not available to compare to the night-shift results. Thus, we do not know whether the improvement seen in the groups that re-entrained was large enough to bring them back to baseline levels. All we can state for certain is that they performed better than the group that did not re-entrain.

In the current study, subjects slept almost as much as possible during the 7-hour daytime dark episode. Nevertheless, it was less time than during baseline, and a partial sleep debt probably built up during the study. It is possible that even greater improvements would have occurred if subjects would have been allowed to sleep longer after the night shifts. However, because we were testing interventions that were designed for real shift workers, we wanted to use a practical, albeit not optimal, daytime dark period.

Previous studies have shown that bright light during the night shift has some alerting effects.[45] One may argue that there was a direct effect of the light pulses we administered during the night shifts that could explain the differences in neurobehavioral measures between the re-entrainment groups. However, the bright light was not administered while the subjects were taking the neurobehavioral battery, and there is little evidence to support any residual effects of bright light on performance, sleepiness, and mood. Furthermore, the subjects in the partial and complete re-entrainment groups performed virtually the same, despite the fact that no one in the partial re-entrainment group was exposed to bright light, while 63% of the subjects in the complete re-entrainment group were exposed to bright-light pulses. Thus, we are doubtful that the direct alerting effect of bright light during the night shift can account for the superior performance in the groups that re-entrained.

Interestingly, in the current study, there were no differences on the night-shift measures between the subjects who were partially re-entrained and those who were completely re-entrained. These data suggest that for young and healthy adults, partial re-entrainment (delaying the Tmin into the first half of sleep) is sufficient to improve the neurobehavioral problems associated with night-shift work. We do not know of any other studies that have compared partial to complete re-entrainment. However, given the results of 2 simulated night-shift studies with similar designs, 1 on young subjects[40] and 1 on middle-aged subjects,[46] we suggest that while partial re-entrainment is sufficient for young subjects, complete re-entrainment may be necessary to reap similar benefits in older subjects.

In many of the neurobehavioral measures, the groups that re-entrained performed better than the group that did not, even on the first night shift. This can be explained by the fact that those who re-entrained started out in baseline and, thus, also on the first night shift, with later circadian phases and thus more re-alignment. However, in some neurobehavioral measures there were no differences between the groups that re-entrained and the group that did not re-entrain until the third night shift. Therefore, one could question whether interventions to produce circadian re-alignment would be worth it for workers who only work 2 or 3 consecutive night shifts and then have some days off. If circadian rhythms phase advanced during the days off, then it could conceivably take another 3 days of night work before the rhythms once again delayed enough to produce sufficient re-alignment to reap substantial benefits. Furthermore, it has been suggested that frequent phase shifts of the circadian clock may not be healthy (see the section "To shift or not to shift" in our review paper.[10])

To address concerns like these, we have designed sleep and light schedules for permanent night-shift workers (see Figure 5 in Eastman & Martin[9] and Figure 4 in Burgess et al[10]). In these schedules, the Tmin is delayed into the beginning of the daytime sleep period and then remains around that phase even during days off. As long as the worker follows a late enough sleep schedule on days off, then the Tmin on days off will occur within sleep, close to the end of the sleep period. Thus, the largest phase shift only happens once, and the circadian rhythms subsequently maintain a compromise phase position between the ideal phase position for night work and the ideal phase position for days off. The ideal phase position in both cases would be for the Tmin to occur about 3 hours before wake-up time. The current results showing that partial re-entrainment is as good as complete re-entrainment, (ie, delaying the Tmin into the first half of sleep is as good as delaying it into the second half of sleep) strengthen the

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rationale for using these types of compromise phase schedules. We are currently testing whether the desired compromise phase position can be maintained in subjects on permanent night-work schedules who alternate between night shifts and days off. Obviously, circadian re-alignment is not possible for rapidly rotating shift-work schedules. However, we have proposed work, sleep, and light schedules designed to keep circadian rhythms aligned with sleep throughout a slowly rotating shift-work schedule.[47] Future studies in actual night workers with outcome measures in addition to sleep and artificial performance tasks, including measures such as adherence rates for various interventions, work and motor vehicle accident rates, productivity, absenteeism, and work-shift satisfaction, will be necessary to determine the real-world applicability of these kinds of schedules.

In conclusion, we have shown that even when young healthy people are "phase tolerant" for sleeping at the wrong circadian phase, they are not phase tolerant for working at the wrong circadian phase. Circadian re-entrainment, the re-alignment of circadian rhythms with the new sleep and work schedule, can help overcome night-shift decrements. We suggest that, for young adults, phase delaying the circadian clock until the Tmin occurs just within the beginning of the daytime sleep period may be sufficient to improve alertness and performance during the night shift.

ACKNOWLEDGEMENTS

We thank Sheri Allen, Stacia Martin, Karen Chuang, Jim Lyda, Steve Gaskill, Anne Lagerlund, Rupal Trivedi and Clifford Gazda for assistance in data collection, and Thomas A. Molina for work on many of the figures. We thank David F. Dinges, PhD, and John W. Powell at the University of Pennsylvania for generously providing the Neurobehavioral Assessment Battery software and Psychomotor Vigilance Test response boxes. Support for this study came from the National Institute of Occupational Health and Safety (NIOSH), Centers for Disease Control and Prevention (CDC) grant R01 OH003954. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of NIOSH or the CDC.

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