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Misaligned core body temperature rhythms impact cognitive performance of hospital shift work nurses

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Abstract

Circadian rhythms greatly influence 24-h variation in cognition in nearly all organisms, including humans. Circadian clock impairment and sleep disruption are detrimental to hippocampus-dependent memory and negatively influence the acquisition and recall of learned behaviors. The circadian clock can become out of sync with the environment during circadian misalignment. Shift work represents a real-world model of circadian misalignment that can be studied for its physiological implications. The present study aimed to test the hypothesis that circadian misalignment disrupts vigilance and cognitive performance on occupationally relevant tasks using shift work as a model. As such, we sought to 1) explore the general effects of night- and day-shift worker schedules on sleep-wake parameters and core body temperature (CBT) phase, and 2) determine whether shift-type and CBT phase impact cognitive performance and vigilance at the end of a 12-hour shift. We observed a sample of day-shift and night-shift hospital nurses over a 10-day period. At the end of three, consecutive, 12-hour shifts (7pm-7am or 7am-7pm), participants completed a cognitive battery assessing vigilance, cognitive throughput, and medication calculation fluency (via an investigator developed and tested metric). Night-shift nurses exhibited significantly greater sleep fragmentation as well as a greater disparity between their wake-time and time of CBT minimum compared to day-shift nurses. Night-shift nurses exhibited significantly slower cognitive proficiency at the end of their shifts, even after adjustment for CBT phase. These results suggest that circadian disruption and reduced sleep quality both contribute to cognitive functioning and performance.

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1. Introduction

Twenty-four hour rhythms in physiology (e.g., core body temperature [CBT], melatonin, and cortisol release) and behavior (e.g., learning, memory, vigilance, cognition, and sleep/wake states) are driven by an endogenous circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Smarr, Jennings, Driscoll, and Kriegsfeld, 2014; Wright, Lowry, and Lebourgeois, 2012). The SCN is essential for maintaining circadian rhythmicity and synchronizing secondary oscillators elsewhere in the brain (*e.g.*, the learning and memory center in the hippocampus) and body (*e.g.*, adrenal gland, liver, heart, etc.) (McEwen and Karatsoreos, 2015; Takahashi, Hong, Ko, and McDearmon, 2008). When social, sleep/wake, and other behavioral patterns become out of sync from the endogenous clock and environment (such as during shift work), resulting circadian misalignment can produce a broad range of negative physiological and neurobehavioral consequences including deficits in hippocampus-dependent learning processes such as information acquisition and recall (Baron and Reid, 2014; Prince and Abel, 2013; Smarr et al., 2014).

Shift work has been shown to produce misalignment between the biological clock and sleep/wake timing (Boivin and James, 2002; Costa et al., 1997; Hennig, Kieferdorf, Moritz, Huwe, and Netter, 1998; Roden, Koller, Pirich, Vierhapper, and Waldhauser, 1993; Sack, Blood, and Lewy, 1992; Weibel, Spiegel, Gronfier, Follenius, and Brandenberger, 1997). Key indicators of the endogenous clock phase in humans are 24-hour rhythms in physiological variables such as melatonin, cortisol, and CBT (Moore-Ede, Sulzman, and Fuller, 1982). Melatonin rhythm phase in night-shift workers exhibits large inter-individual variability even when measured after the last night-shift worked in permanent night-shift workers (Weibel et al., 1997) or after 12 days of night shift (Boivin and James, 2002). In one report, cortisol rhythms took five consecutive shifts to adapt to the new behavioral sleep phase, and even then, 25% of the workers’ rhythms never adapted (Hennig et al., 1998). Even consecutive night shifts are insufficient to align melatonin and cortisol rhythms to the new sleep/wake phase (Costa et al., 1997; Roden et al., 1993; Sack et al., 1992).

Circadian misalignment has been associated with pronounced negative effects on shift workers’ sleep, sleepiness, performance, concentration, attention, memory, and accident risk (Akerstedt and Wright, 2009; Karatsoreos, 2012), which may be attributable in part due to disruption of core body temperature rhythms. Previous research has established the existence of a positive relationship between daily rhythms of body temperature and cognitive performance and alertness in humans (Carrier and Monk, 2000; Kleitman and Jackson, 1950; Kleitman, Titelbaum, and Feivenson, 1938; Lavie, 1980; Wright, Hull, and Czeisler, 2002; Valdez, Ramirez, & Garcia, 2012). More recent studies have utilized a forced desynchrony protocol (consisting of a 28-hour sleep/wake cycle, which is outside the human circadian clock’s range of entrainment) to examine the relationships among circadian phase, CBT amplitude (independent of circadian phase), duration of wakefulness, and cognitive performance (Dijk, Duffy, and Czeisler, 1992; Wright et al., 2002). Results from these studies have supported that increased CBT contributes to improved cognitive performance and alertness – independent from its association with circadian phase (Dijk et al., 1992; Wright et al., 2002). Cognitive performance tends to decrease across the day as a function of time spent awake, with worst performance occurring at night near the minimum of the body temperature rhythm (Czeisler, Dijk, and Duffy, 1994; Dijk et al., 1992; Wright et al., 2002). Although acute sleep restriction negatively impacts vigilance, cognitive performance, and sleep recovery (Banks and Dinges, 2007), rhythms in vigilance/alertness and cognitive function persist even under conditions of chronic sleep deprivation, suggesting that circadian drive for these processes is independent from the homeostatic sleep process (i.e., “sleep debt”) (Goel, Basner, Rao, and Dinges, 2013).

To date, the majority of studies investigating the influence of circadian misalignment and sleep on neurobehavioral processes have utilized experimental research designs undertaken in highly controlled laboratory conditions. The shiftwork environment provides a real-world context useful for further investigating the relationships present among circadian processes, sleep, and cognitive performance. Hospital shift-work nurses represent a particularly important cohort to study because their alertness and performance is crucial for patient safety, and they are often subjected to highly irregular schedules. The primary intent of the current study was to examine how cognitive performance is affected by circadian misalignment within the real-world context of hospital shiftwork. Toward this aim, our sample consisted of day- and night-shift nurses working a standard 12-hour hospital shift schedule, and our measures of cognitive performance included an occupationally-relevant medication calculation task in addition to measures of cognitive proficiency (ADD) and vigilance (PVT). For this study, circadian misalignment was defined as a disrupted phase relationship between the time of CBT minimum and wake-up time. During circadian alignment, the CBT minimum typically occurs approximately one and a half to three hours before waking each night (James, Boivin, Charbonneau, Bélanger, and Cermakian, 2007; Czeisler, Johnson, Duffy, Brown, Ronda, and Kronauer, 1990). The specific aims of the current study were to 1) explore the general effects of night- and day-shift schedules on sleep-wake parameters and CBT phase, and 2) determine whether shift-type and CBT phase impact cognitive performance and vigilance at the end of a 12-hour shift. We hypothesized that night-shift nurses would exhibit greater circadian misalignment and sleep disturbance than day-shift nurses, and that these disruptions would result in more impaired cognitive performance.

2. Materials and Methods

2. 1. Participants

Inclusion Criteria: Participants were female, day-shift and night-shift nurses recruited from a large university medical center in the Southeastern United States who were (a) employed full-time (> 36 hours per week) as a registered nurse, (b) ≥19 years old, and (c) had at least a 3-week history of their current shift assignment (night-shift or day-shift). Participating nurses self-selected their shift schedule (day-shift versus night-shift). This naturalistic study design (rather than randomized assignment) was selected to minimize disruption to the hospital unit’s scheduling processes. Chronotype was calculated by using midsleep time on days off with sleep debt correction (as in Petrov et al., 2014) and categorized into earlier and later chronotypes (by median chronotype). In this particular sample, there were 15 participants with early chronotype (9 in day shift and 6 in night shift) and 15 participants with late chronotype (9 in night shift and 6 in day shift), resulting in no significant difference in the proportion of workers who were considered later versus earlier chronotypes across shift types (Fisher's Exact Test, $p = 0.47$). During the study period, eligible day-shift nurses and night-shift nurses were required to be assigned to three consecutive work shifts falling within one hour of 7 AM – 7 PM and 7 PM – 7 AM, respectively. Night-shift nurses had the additional criterion of sleeping primarily during the night while off-work (rather than maintaining daytime sleep during work and off-work). This criterion was included to reflect findings from a previous study conducted among nurses in this hospital, which found that approximately 97% of night-shift nurses preferred to switch to sleeping at night on their off-shift days (Petrov et al., 2014). This criterion was also intended to reduce variability in adaptation to shift work attributable to sleep strategy, as nurses who maintain daytime sleeping while off-work tend to be more adapted to shift work than nurses who switch their sleep schedules on days-off (Petrov et al., 2014). Sleep strategy was determined during preliminary screening via a survey question asking nurses to indicate their preferred sleep time on off-work days (and confirmed retroactively via their actigraphy records).

Exclusion Criteria: Both day- and night-shift nurses were excluded from participation if they (a) were pregnant or nursing, (b) were currently working multiple jobs, (c) screened positive for a psychiatric illness or substance abuse (determined by MINI International Neuropsychiatry Interview; MINI), (d) reported a diagnosis of a primary sleep disorder other than shift work sleep disorder, (e) reported habitual smoking, and (f) reported current use of tranquilizers or sleep aid medication. Men, who represent 15% of University of Alabama at Birmingham Hospital staff nurses, were excluded from analysis to reduce sex-related variability (Cain et al., 2010) and increase statistical power.

Informed Consent: A HIPAA waiver of informed consent was granted for screening participants. Once the participant met the pre-screening eligibility criteria, an informed consent protocol was administered by a research assistant trained in the ethical conduct of human research to ensure that participants provided truly voluntary and informed consent.

Compensation: Participants received $30 each for the initial visit and an additional $70 each at the end of the 10-day assessment.

Procedures: After giving informed consent, participants were scheduled for an initial appointment in the Office of Psychiatric Clinical Research on the morning of the first full day off. On Study Day 1, nurses were instructed in the use of the Actiwatch and Vitalsense monitors and were trained on the cognitive tests (the addition test [ADD] and drug calculation test [DRUG]) and the neurobehavioral measure (Psychomotor Vigilance Test [PVT]). The 10-day study consisted of 3 consecutive days off, 3 work days, and 4 consecutive days off for day-shift nurses (7AM–7PM) or 4 consecutive days off, 3 work days, and 3 days off for night-shift nurses (7PM-7AM). During the study, participants completed daily sleep diaries, indicating their sleep and wake-up times. At the end of each 12-hour shift (approximately 7 am for night-shift nurses, 7 pm for day-shift nurses), a research staff member met each participant at work and administered the ADD, DRUG, and

PVT measures via a laptop computer. All participants were asked to refrain from alcohol during the entire 10-day assessment.

2.2. Instruments and Devices

A. Mini-International Neuropsychiatry Interview (MINI) was used to screen for psychiatric illness and substance abuse.

B. Sleep-Wake Diaries (Manber, Bootzin, Acebo, and Carskadon, 1996) were used by the study subjects to record start and end times of all sleep periods, including naps.

C. Respironics VitalSense and Actiware. The Actiwatch-Spectrum (Respironics, Inc., Murrysville, PA) measured continuous movement and irradiance (three color bands of the visible spectrum). Actiware version 5.04 (Respironics, Inc., Murrysville, PA) was used to calculate sleep parameters in conjunction with the sleep-wake diary to determine time in bed. Sleep parameters measured with the Actiware software included sleep duration, sleep efficiency, wake after sleep onset (WASO), percent wake (during sleep session), and sleep fragmentation. Sleep duration was defined as the time (hours) between sleep onset and offset. Midsleep time was calculated as the midpoint between sleep onset and sleep offset based on data from both sleep diary report and actigraphy analysis.

CBT was recorded every minute with ingestible capsules that were telemetrically connected to a VitalSense monitoring device (Respironics, Inc.; see McKenzie and Osgood, 2004), and the estimated CBT minimum was quantified and analyzed for each participant with cosinor analysis (Xu et al., 2009). Specifically, we fitted a cosinor wave to the 24-hour CBT interval immediately preceding the time of test administration on each of the nurse’s three shifts. Cosinor analysis was only performed in cases where there were at least 24-hours of CBT data preceding a given testing time. Outliers were identified and removed from each CBT record prior to cosinor analysis via a two-step procedure. First, large spikes and dips in the temperature record attributable to new sensor ingestion or lost data were removed. Second, acute spikes or dips falling outside of a normative range of temperatures (typically between 35.5 and 38.5 degrees Celsius) were removed if they deviated from the average temperature trend within a given hour of data. Five cycles of CBT data were excluded due to arrhythmicity during the 24-hour period preceding testing, which precluded the ability to establish a reliable and accurate phase reference point.

The fitted cosinor wave was used to determine (1) temperature amplitude (°C), (2) the timing of each nurse’s temperature minimum (trough time), and (3) the timing of each nurse’s temperature maximum (peak time). The phase angle between timing of nurses’ CBT minimum and nurses’ wake time was calculated (absolute value of degrees) as an indicator of circadian misalignment. CBT maximum was used as an indicator of predicted time of optimal cognitive performance based on research supporting the positive relationship between these two variables (Carrier and Monk, 2000; Dijk et al., 1992; Kleitman and Jackson, 1950; Lavie, 1980; Wright et al., 2002; Valdez et al., 2012). The phase angle between timing of nurses’ CBT maximum and the time of testing (CBT_{max}-test phase angle) was calculated in degrees (absolute value) to provide an indicator of how far each nurse was from her optimal performance time during testing.

D. Psychomotor Vigilance Test (PVT; http://buypvt.com/) was used to measure sustained attention and reaction time (Thorne, Johnson, Redmond, Sing, Belenky, and Shapiro, 2005). This test, well known for its sensitivity to sleep deprivation and circadian regulation, was administered via a laptop computer with the necessary hardware and software specifications for PVT administration. Subjects responded to randomly spaced stimuli, and data were electronically gathered on lapses (responses > 500 ms) and median reaction times (Geiger-Brown and Trinkoff, 2010).

E. The Two-Digit Addition Test (ADD), a standardized test, was used to measure cognitive throughput via speed and accuracy of responses (Wright, Hull, Hughes, Ronda, and Czeisler, 2006). This test presented the participant (via laptop computer) with a series of randomly generated pairs of two-digit numbers from left to right in a single row (e.g., 23 + 43). The test was scored according to the number of correct calculations over a 2-minute period. Participants were told, “Speed and accuracy are equally important.” The number of correct responses was calculated as the primary measure, but number of problems attempted, reaction time, and answer were also recorded. Importantly, participants were given a practice session on Day 1 in order to avoid the steep part of the learning curve during data collection on subsequent days. Practice trials continued until participants achieved 90% accuracy and performance did not change by more than 10% from trial to trial (this took 5–10 trials).

F. Drug Calculations (DRUG CALC) was used as a measure of cognitive performance that required the subject to compute a series of 10 simple medication calculations, randomly selected without replacement for any given day from a test bank of 40 possible calculations. As with the ADD, this test was computerized. The score was calculated as the average number of correct responses per minute. The computerized neurobehavioral tests (D, E, & F) took < 20 minutes to complete.

2.4. Statistical Analysis

Data analysis was conducted using SPSS v. 24. Nonlinear cosinor analysis was used to fit the CBT data for each subject and determine the phase angle (in relation to wake onset) and trough CBT (as in (Xu et al., 2009)). Circular statistics and Rayleigh vector plots were performed (Oriana 2.0) on the CBT phase data within each group to determine the amount of phase variability present within each shift type. To determine effects of shift group on performance, separate multilevel models were constructed for each variable of interest: ADD average time per problem, ADD number correct, DRUG total completion time, PVT lapses, and PVT median reaction time. Statistical models used a two-level repeated measures structure using the SPSS MIXED procedure with shifts (level 1) nested within individuals (level 2). Variables of interest included shift type (level 2), CBT_{max}-test phase angle (level 1), and the cross-level interaction of these two factors. This same model was used to determine whether shift type interacted with work-day actigraphy outcomes (sleep duration, sleep efficiency, sleep fragmentation, WASO, and percent wake). Only day-shift nurses and night-shift nurses who had complete Actigraphy data for each day of data collection were included when analyzing the effect of shift-type on sleep parameters (N = 14 day-shift nurses and 14 night-shift nurses).

3. Results

Participant Characteristics

A total of 31 participants were enrolled in the study. One participant was terminated from the study for failure to comply with procedures, yielding a final sample size of 30 nurses (15 day-shift nurses and 15 night-shift nurses). The average age of participants was 31.2 years (with a range of 22 to 56 years). There were no statistically significant differences in age between day-shift and night-shift nurses ($t(28) = 1.32$, $p = .90$). There were also no significant differences between day-shift nurses and night-shift nurses with respect to experience with the current schedule (Median = 0.9 years for day-shift nurses versus and 1.08 years for night-shift nurses) or racial distribution (3 out of 15 day-shift nurses were African American versus 6 out of 15 night-shift nurses were African American).

Effect of Shift Schedule on Sleep-Wake Parameters

To determine general effect of shift schedule on sleep-wake parameters, we compared day-shift nurses and night-shift nurses on a variety of actigraphic parameters. For night shift nurses, sleep duration was of notably short duration (< 6 hours) across work days and days off ($p = .06$; Table 1). On days off, night shift nurses slept approximately 2 hours less than day shift nurses (Table 1). On work days, night-shift nurses exhibited significantly less WASO (minutes) despite increased sleep fragmentation compared to days off (Table 1).

Effect of Shift Schedule on Circadian Phase

As an internal circadian phase marker, we determined the timing of day-shift versus night-shift nurses' CBT minimum ($\mathrm{CBT}_{\mathrm{min}}$) for each work day. Figure 1 provides a representative CBT trace (with cosinor fit line) for Shift 1 and Shift 2 for a day-shift nurse (A) and night-shift nurse (B). As shown in Figure 2, the time of the $\mathrm{CBT}_{\mathrm{min}}$ was significantly later in night-shift nurses compared to day-shift nurses during each work shift (Watson-Williams F test, $p < 0.01$). Compared to day-shift nurses, the phase angle between night-shift nurses' $\mathrm{CBT}_{\mathrm{min}}$ time and their wake time (henceforth referred to as the $\mathrm{CBT}_{\mathrm{min}}$-wake phase angle) was significantly greater on the second ($t[11] = 2.53$, $p < 0.05$) and third ($t[10] = 2.48$, $p < 0.05$) work shifts but not the first work shift ($t[8] = 0.54$, $p = 0.60$). Specifically, the mean (± SEM) $\mathrm{CBT}_{\mathrm{min}}$-wake phase angle (in decimal hours) for Days 1, 2, and 3 in day-shift nurses was 3.42 (± 1.26), 2.21 (± 0.59), and 3.62 (± 0.53), respectively. For night shift nurses, the average CBTmin-wake phase angle was 4.34 (± 1.09), 6.88 (± 1.37), and 6.31 (± 0.95) for Days 1, 2, and 3, respectively. Although the $\mathrm{CBT}_{\mathrm{min}}$ time was later for night-shift nurses relative to day-shift nurses, it is important to note that for the majority of shifts, $\mathrm{CBT}_{\mathrm{min}}$ occurred before the onset of sleep (approximately 10:20 AM for night-shift nurses during work; Table 1), strongly suggesting that even by the third night shift, these night-shift nurses remained misaligned.

Effect of Shift Schedule and Circadian Phase on Cognitive Performance

We next sought to explore how shift-type (day-shift versus night-shift) and CBT timing interacted to impact performance on three cognitive tasks. The timing of nurses' CBT maximum/peak (CBT_{max} as determined via the cosinor analysis fit to the 24-hours of data preceding testing) was used as an indicator of predicted time of optimal cognitive performance. The phase angle between CBT_{max} and time of testing (the CBT_{max}-test phase angle) was calculated for each nurse and each shift. Using separate linear mixed models, each cognitive task (PVT, ADD, and DRUG) was regressed on predictors of (1) shift-type (day-shift versus night-shift), (2) CBT_{max}-test phase angle, and (3) the interaction of these predictors (shift-type × CBT_{max}-test phase angle). Separate models were used to determine whether shift-type interacted with work-day actigraphy outcomes (sleep duration, sleep efficiency, sleep fragmentation, WASO, and percent wake) to influence cognitive test performance. Significant results are presented for each cognitive task in the proceeding subsections.

Addition Task.—As a measure of cognitive proficiency, the ADD task can be measured in terms of average time to complete each problem or as the total number of problems completely correctly in the allotted time (2 min). For both the total number correct and completion time, there were significant interactions of shift-type by CBT_{max}-test phase angle ($F[1,40] = 11.61$, $p < 0.01$, and $F[1,40] = 9.28$, $p < 0.01$, respectively, Figure 3A). Among day-shift nurses, nurses with a greater CBT_{max}-test phase angle (indicating larger discrepancy between testing time and CBT peak time) tended to answer fewer addition problems correctly and required more time to answer each problem. Night shift nurses, however, exhibited the opposite relationship. Among night-shift nurses, a greater CBT_{max}-test phase angle was associated with a greater number of addition problems answered correctly. There was no consistent relationship between CBT_{max}-test phase angle and time to complete each addition problem for night-shift nurses. It is important to note that independent of CBT_{max}-test phase angle, night-shift nurses correctly completed fewer problems and took longer to complete each problem compared to day-shift nurses when tested after each work shift (main effect for shift-type: total correct, $F[1,40] = 11.07$, $p < 0.01$; completion time, $F[1,40] = 9.28$, $p < 0.01$).

When actigraphic measures were explored, average sleep duration before each work shift was found to interact with shift-type to predict ADD-number correct (shift-type main effect, $F[1,84] = 5.91$, $p < 0.05$; shift-type × sleep-duration, $F[1,84] = 7.58$, $p < 0.01$). The number of problems completed correctly increased with the amount of sleep for day-shift nurses (Figure 4A), while no consistent relationship between sleep duration and ADD-number correct was observed for night shift nurses (Figure 4B). A similar interaction and trend were observed for the percentage of time spent awake during the sleep interval and ADD-total correct (shift-type main effect, $F[1,83] = 6.58$, $p < 0.05$; shift-type × percent time spent awake, $F[1,83] = 5.02$, $p < 0.05$). Increased time awake was associated with decreased number of correct ADD items for day-shift nurses but not in night-shift nurses (data not shown).

Drug Calculation Task.—As a more occupationally-relevant performance measure, we also administered a brief, 10-question, multiple choice medication calculation fluency test (DRUG CALC). The questions were designed to be easy enough that the correct answers were likely to be selected by all nurses. Thus, there was no difference in the number of problems completed correctly by day-shift nurses versus night-shift nurses (data not shown). However, the time to complete the 10-question test was significantly different between day-shift nurses and night-shift nurses (main effect for shift-type, F[1,40] = 4.63, $p < 0.05$). Moreover, for the outcome of DRUG CALC completion time, there was a trend for the interaction of shift-type by CBT_{max}-test phase angle (F[1,40] = 3.95, $p = 0.054$). A greater CBT_{max}-test phase angle tended to be associated with increased completion time (Figure 3B).

Psychomotor Vigilance Task.—Lastly, we examined whether there was an effect of shift-type, CBT_{max}-test phase angle, or actigraphic measures on nurses' performance on the widely used PVT (10-min). The CBT_{max}-test phase angle did not predict PVT reaction time or lapses for either day-shift or night-shift nurses (data not shown). Notably, the number of lapses was not found to vary by shift-type. When actigraphic measures were explored, analysis revealed a significant main effect of sleep efficiency on PVT median reaction time (F[1,67] = 5.26, $p < 0.05$); however, there was no effect of shift-type or the interaction of shift-type by sleep efficiency ($p > .25$ for both).

4. Discussion

In this paper, we aimed to 1) explore general effects of shift schedule on sleep-wake parameters and circadian phase, and 2) determine whether shift type, circadian phase, and sleep parameters collectively impacted occupationally relevant performance outcomes of cognitive proficiency (ADD), vigilance (PVT), and medication calculation fluency (DRUG CALC) at the end of a 12-hour shift. First, we showed that night-shift nurses exhibit greater sleep fragmentation as well as greater disparity between wake-time and time of CBT minimum on work days than their day-shift counterparts. Second, we demonstrated that, compared to day-shift nurses, nurses working night-shift exhibit comparable vigilance but distinctly slower cognitive proficiency after a 12-hour shift.

Shift work has been shown to produce misalignment between the biological clock and sleep/wake timing (Boivin and James, 2002; Costa et al., 1997; Hennig et al., 1998; Roden et al., 1993; Sack et al., 1992; Weibel et al., 1997), which has been associated with pronounced negative effects on shift workers' sleep, sleepiness, performance, and accident risk as well as numerous health outcomes (Akerstedt and Wright, 2009). In the present study, we found that – compared to day-shift nurses – night-shift nurses exhibited a significantly greater discrepancy between their time of CBT minimum and wake-time during their second and third shifts, indicating the presence of greater misalignment on these days. In fact, night-shift nurses' CBT minimum occurred before the onset of sleep in over half of these shifts, a state that has been used to define circadian misalignment in astronauts (Flynn-Evans, Barger, Kubey, Sullivan, and Czeisler, 2016). Thus, the use of telemetry to measure CBT in field settings could potentially be used as a circadian misalignment biomarker in shiftworkers that is more easily implemented than salivary melatonin (due to light-suppressive effects).

In addition to circadian misalignment, sleep disruption has been cited as a principal factor contributing to deficits in performance among night-shift workers (Mitler et al., 1988). The present study found that night-shift nurses experienced greater sleep fragmentation (but not wake after sleep onset) on their work nights compared to day-shift nurses. Night-shift nurses were also found to attain approximately 2 fewer hours of sleep than day-shift nurses on their days off, a finding which may be explained – at least in part – by the often detrimental sleep strategies night-shift nurses utilize when transitioning from sleeping during the night to sleeping during the day (Gamble et al., 2011). For example, a previous study conducted among a cohort of night-shift nurses from the same hospital revealed that approximately 1 in 5 nurses switch from days to nights (and vice versa) by choosing an approximately 24-hour period to stay awake (often immediately prior to or following their first shift), despite this being one of the most detrimental strategies in terms of health and wellbeing (Petrov et al., 2014). Future studies are necessary to ascertain the impact of various sleep strategies on sleep-related impairments among shift workers.

The current study revealed that night-shift nurses exhibited slower cognitive proficiency, as evidenced by their decreased accuracy and lengthened response time on the addition task, as well as their lengthened response time on the medication calculation task. Additionally, among day-shift nurses only, nurses who exhibited a greater discrepancy between testing time and time of their CBT maximum/peak (a greater $\mathrm{CBT}_{\mathrm{max}}$-test phase angle) tended to answer fewer addition problems correctly and required more time to answer each problem. This result was consistent with human experimental findings, which have supported relationships among increased CBT, internal biological synchrony, and neurobehavioral performance and alertness (Akerstedt, Froberg, Friberg, and Wetterberg, 1979; Dijk et al., 1992; Kleitman and Jackson, 1950; Kleitman, 1938; Lavie, 1980). Surprisingly, night-shift nurses exhibited the opposite relationship; a greater $\mathrm{CBT}_{\mathrm{max}}$-test phase angle corresponded to a greater number of addition problems completed correctly, although performance was still largely below the level of most day-shift nurses. This result suggests that more work is necessary to determine the confounding factors that may mask the CBT phase during a state of circadian misalignment in the absence of controlled laboratory conditions.

Previous research has indicated the presence of an association between night shift work, sleepiness, and impaired vigilance (Narciso et al., 2016). When comparing night-shift nurses to day-shift nurses in the current study, we failed to detect a meaningful difference between these two groups on any of the PVT parameters investigated. This finding, while contradictory to our initial hypothesis, is consistent with research conducted by Geiger-Brown and colleagues (2012) which also detected no significant differences between day- and night-shift in the mean reaction time or number of lapses on a 5-minute PVT test. Rather, the authors reported that PVT variable lapses appeared to represent a trait-like variable, with some nurses conceivably predisposed to greater sleep-related lapses of vigilance, regardless of shift-type (Geiger-Brown et al., 2012). Additionally, night-shift workers' reliance on caffeine to sustain performance for the duration of their 12-hour shift may have mitigated observed shift-related differences in PVT performance attributable to sleepiness. However, due to concerns regarding nurse and patient safety, limiting caffeine consumption in the current study was neither desirable nor feasible. Lastly, given the relatively small magnitude of documented differences in PVT parameters over consecutively worked shifts (Geiger-Brown et al., 2012), it may be the case that the relatively small nature of our sample possessed insufficient power to detect a statistically significant difference between our two groups on these outcome measures.

The ADD and DRUG CALC tasks, relative to the PVT, place higher demands on the combination of working memory and processing speed, which may help to explain the shift-related discrepancies observed on these cognitive performance measures. Kretschmer and colleagues (2013) have demonstrated that bright light has a strong direct and independent effect on the cognitive performance parameters of working memory and concentration among shift workers. This beneficial effect of bright light on cognitive performance among shift workers may be due to enhanced entrainment of the central pacemaker in suprachiasmatic nucleus (SCN), allowing better adaptation to shift work. On the other hand, another randomized controlled trial for the efficacy of blue-enriched polychromatic light in night workers failed to ameliorate circadian misalignment (Sletten et al., 2017). Thus, future research is warranted to explore interventions and behavioral strategies to further alleviate the negative impact of circadian misalignment, sleep loss, and poor sleep quality on shift workers' cognitive performance, health, and overall wellbeing.

Previous studies examining the relationships between circadian processes and cognitive performance have demonstrated the utility of CBT as a reliable phase marker in humans (Dijk et al., 1992; Wright et al., 2002). Additionally, experiments conducted in animal models have established CBT as a useful biomarker of circadian misalignment. Karatsoreos et al. (2011) modelled the effects of chronic circadian misalignment in mice (via a 20-hour light/dark cycle outside their range of entrainment) and found that their CBT fluctuated between states of entrainment and arrhythmicity (Karatsoreos et al., 2011). Circadian disruption in these animals was linked to decreases in cognitive flexibility and negative impacts on neuronal and brain architecture in the prefrontal cortex, which is one of the primary brain regions responsible for higher-order cognitive tasks such as executive function (i.e., attention and working memory, etc.) and emotional control (Karatsoreos et al., 2011). However, an important limitation in the present field study is that CBT amplitude can be influenced by additional factors that 'mask' CBT rhythms controlled by the internal circadian clock, such as time spent awake, exercise, taking a hot bath/shower, etc. (Moul, Ombao, Monk, Chen, and Buysse, 2002; Waterhouse et al., 2000). Despite this consideration, our results point to the utility of CBT rhythms to predict performance in day-shift workers but not night-shift workers. One reason that CBT phase may not have predicted performance well among night-shift nurses in the present study is that night-shift nurses' testing was conducted at the end of the 12-hour night-shift at a time when nearly all of these nurses were far from their CBT peak (when performance is maximized). Future studies that examine performance at earlier phases of the circadian cycle may find different results.

With regard to our findings, several considerations warrant mention. All nurses in the sample worked standardized shifts during the study period and were recruited from the same hospital, thereby reducing variability within the groups attributable to work schedule and environment. The primary limitation of this study is its small sample size, which may have limited statistical power to detect meaningful shift-type differences. The small sample size also limited the feasibility of applying Type I error corrections for multiple comparisons, which should be considered when deriving overall conclusions. For example, while there were some significant differences between night-shift and day-shift on sleep-wake parameters, most variables were not significantly different, favoring that sleep may be largely unaffected by shift-type in the current study. An additional limitation of the current study is its observational nature, wherein participants self-selected their shift assignment. Self-selection of shift-type introduces the possibility that nurses may have preferentially chosen to work shifts scheduled at a time-of-day that coincided with their chronotype, which could have mitigated the extent of circadian misalignment observed in the current study. However, we found no significant differences in the proportion of earlier versus later chronotypes (based on median sleep-debt corrected midsleep time; Petrov et al., 2014) in day shift versus night shift.

The findings of the present study provide important novel results regarding the relationship between shift work, circadian disruption, and cognitive performance, which will hopefully inform future initiatives aimed at improving the wellbeing of the shift work population. Another unique contribution of this study is the creation of an occupationally-relevant measure of cognitive performance (the DRUG CALC) for the staff nurse population.

5. Conclusions

The findings of this study suggest that shiftwork-induced circadian and sleep disruption is associated with impaired cognitive performance in shift workers. The results of the current study, combined with the existing literature on acute and persisting effects of cognitive impairment among shift workers, have important implications for not only patient safety by also occupational health policy. This study also points to circadian misalignment as a potential target for future interventions aimed at mitigating the influence of shift work on cognitive performance, including memory and learning processes. Given that 7 to 15% of American workers are shift workers or work an alternative work schedule (National Sleep Foundation, 2008; United States Department of Labor, 2005), these research findings have important implications beyond the nursing field and findings may impact shift workers in other fields, such as the automotive and trucking industries, whose jobs require sustained alertness and vigilance.

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Highlights

- Night-shift fragmented sleep that was misaligned with temperature rhythms.
- Night-shift slowed performance on cognitive proficiency tasks by the shift end.
- Core body temperature of shift workers may predict cognitive performance.

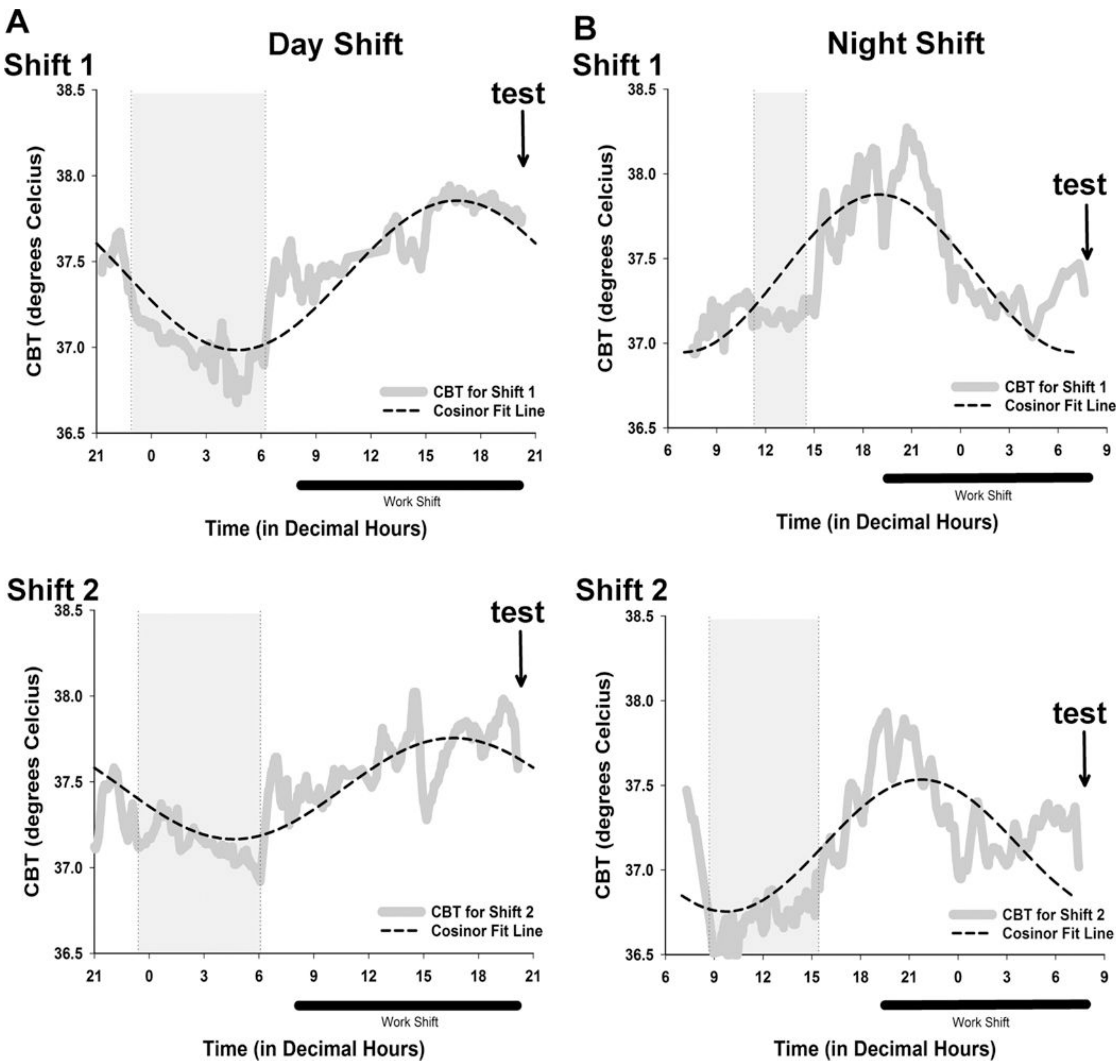

Figure 1. Representative 24-hour CBT trace for Shift 1 (top) and Shift 2 (bottom) for a day-shift nurse (A) and night-shift nurse (B).

Cosinor fit line indicated via dashed line. The sleep period for each day is shaded in grey. An arrow specifies the time that cognitive tests were administered during the work shift (indicated via the black horizontal bar).

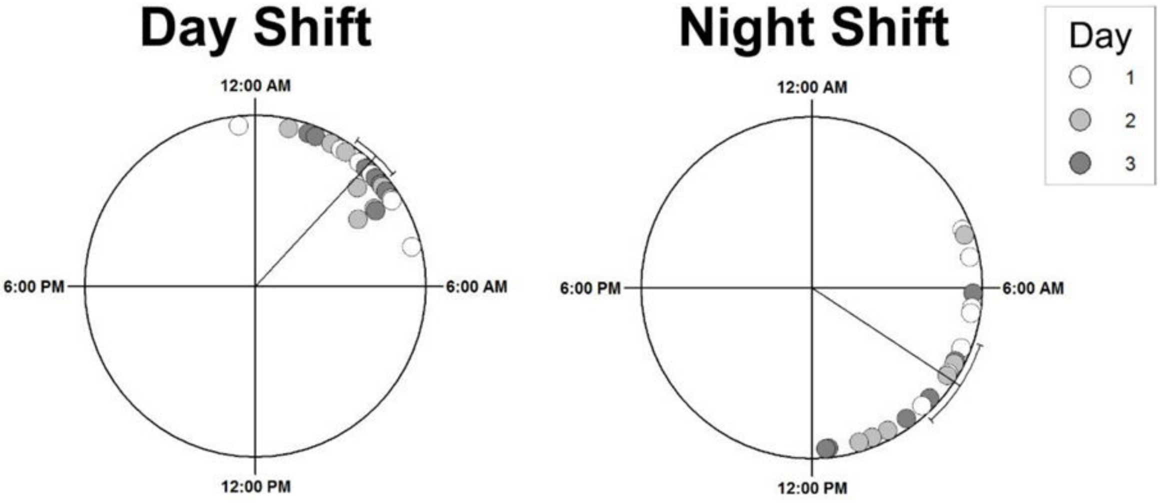

Figure 2. Rayleigh vector plots of times of the CBT minimum for day-shift and night-shift nurses across three consecutive work shifts.

CBT phase for day-shift nurses and night-shift nurses are shown across three consecutive work days (shown in greyscale). Nonlinear cosinor analysis was used to fit the CBT data for each subject and determine the phase angle (in relation to wake onset) and trough CBT.

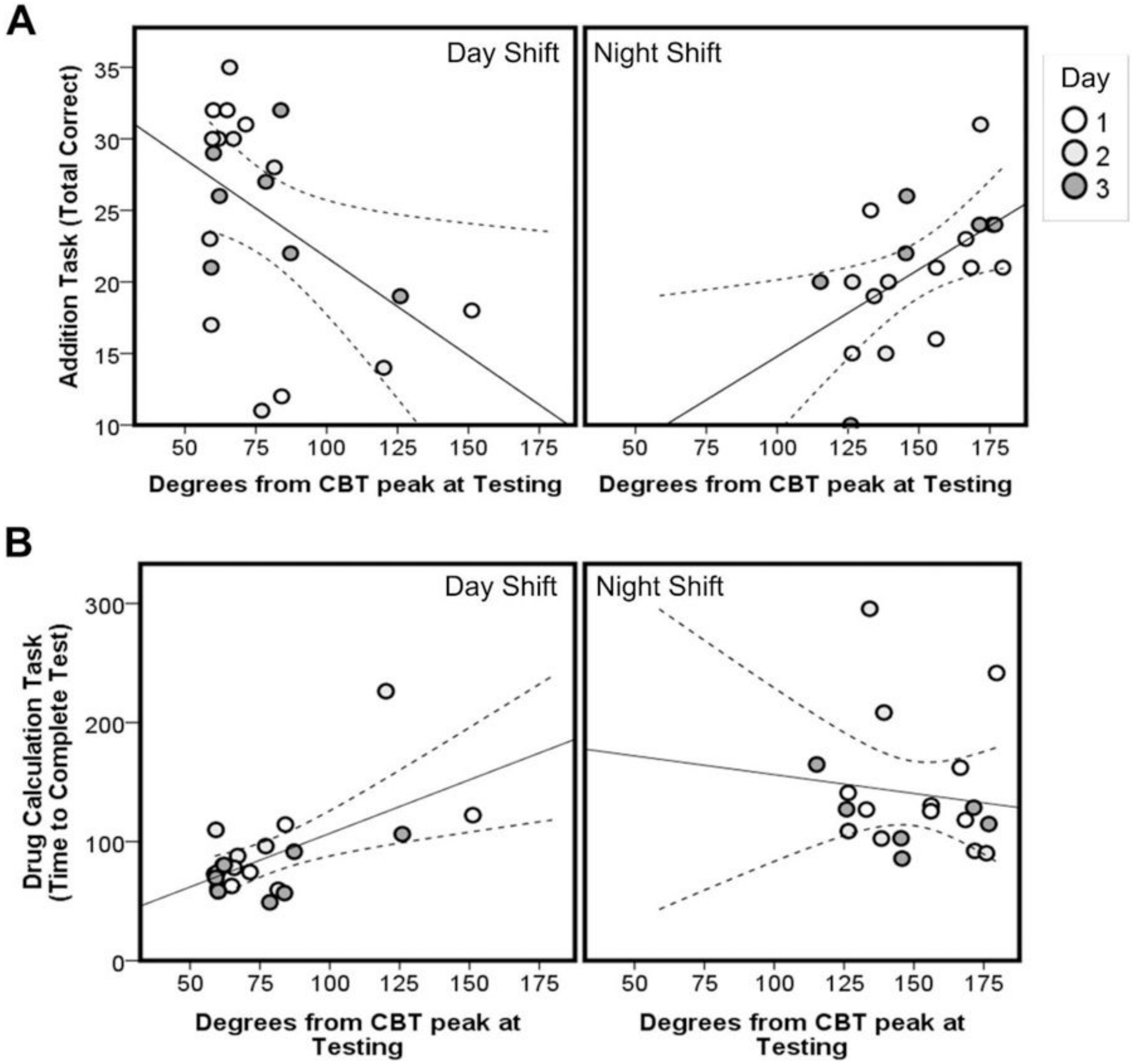

Figure 3. Linear relationship between degrees from CBT maximum/peak at testing and performance measures of cognitive throughput (A) and medication calculation fluency (B) for day-shift and night-shift nurses across three consecutive work shifts.

Separate multilevel models were constructed with the variables of shift-type, CBT distance from peak at testing, and the interaction of these terms predicting each of the cognitive performance variables of interest (ADD, PVT, and DRUG CALC). For both the total number correct and completion time (not shown), there were significant interactions of shift type by CBT-degrees (A, SHIFT X CBT interaction for ADD-total correct: F[1,40] = 11.61). Similarly, there was a trend for DRUG-time to interact with CBT-degrees (B, F[1,40] = 3.95, p = 0.054) with increased completion time with greater degrees away from the CBT predicted peak in day-shift nurses but not night-shift nurses.

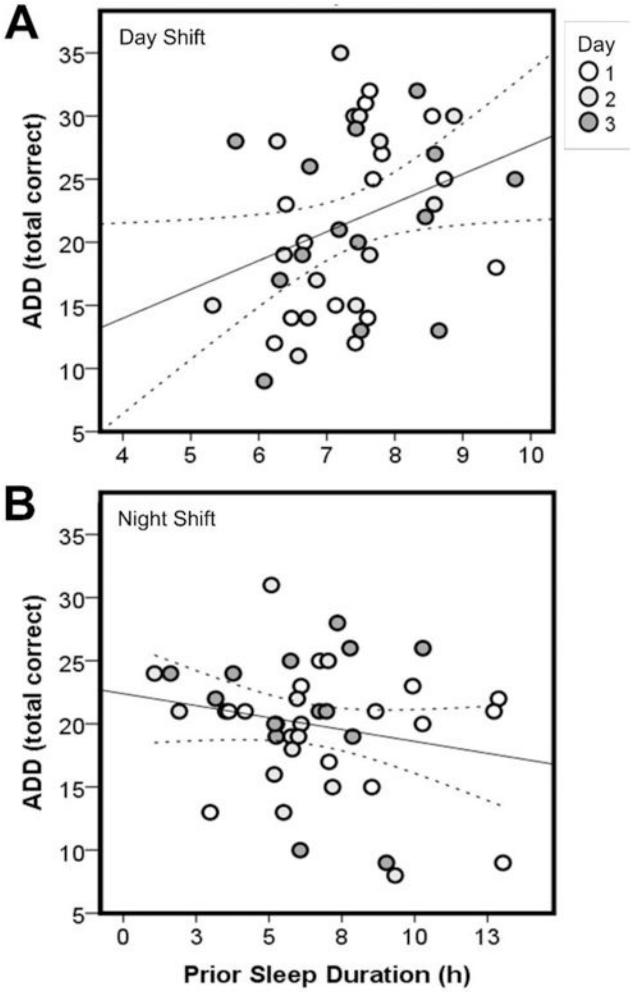

Figure 4. Linear relationship between prior sleep duration and cognitive throughput for day-shift and night-shift nurses.

Separate multilevel models were constructed with the variables of shift-type, prior sleep duration, and the interaction of these terms predicting each of the cognitive performance variables of interest (ADD, PVT, and DRUG CALC). The number of problems completed correctly on the ADD task increased with the amount of sleep for day shift nurses, while no consistent relationship existed between sleep duration and ADD-number correct for night shift nurses (SHIFT main effect: F[1,84] = 5.91, $p < 0.05$; SHIFT X SLEEP-DUR: F[1,84] = 7.58, $p < 0.01$).

Table 1.

Actigraphic parameters for Day Shift (N = 14) and Night Shift (N = 14). Mean (SEM).

Shift	**Sleep Onset**	**Sleep Offset**	**Sleep Duration**	**Mid-sleep Time**	**Sleep Efficiency**	**Wake After Sleep Onset (WASO)**	**Percent Wake**	**Fragmentation**
Work Day (Shift 2)								
Day	23.3 (0.2)	6.0 (0.2)	6.7 (0.2)	2.7 (0.2)	8 9.2 (1.1)	30.3 (2.7)	7.7 (0.6)	1 2.4 (1.7)
Night	10.3 (0.4) *	15.8 (0.5) *	5.5 (0.5)	13 (0.3) *	78.4 (6.4)	20.8 (3.2) *	7.3 (1.4)	20.8 (3.4) *
Off Work								
Day	0.3 (0.6)	8.2 (0.5)	7.9 (0.4)	4.2 (0.5)	85.6 (1.2)	45.8 (4.8)	9.5 (1.0)	17.7 (1.5)
Night	2.7 (0.7) *	8.5 (0.6)	5.8 (0.8) *	5.6 (0.5)	80.8 (4.1)	36.0 (7.7)	8.7 (1.4)	20.6 (2.9)

Note: Time is reported in decimal hours.

* $p < 0.05$, Day Shift vs. Night Shift