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## Sleep and Circadian Variability in People with Delayed Sleep-Wake Phase Disorder versus Healthy Controls

Helen J. Burgess<sup>a</sup>, Margaret Park<sup>b</sup>, James K. Wyatt<sup>b</sup>, Muneer Rizvydeen<sup>a</sup>, and Louis F. Fogg<sup>c</sup>

<sup>a</sup>Biological Rhythms Research Laboratory, Department of Behavioral Sciences, Rush University Medical Center, Chicago, Illinois USA

<sup>b</sup>Section of Sleep Disorders and Sleep-Wake Research, Department of Behavioral Sciences, Rush University Medical Center, Chicago, Illinois USA

<sup>c</sup>College of Nursing, Rush University Medical Center, Chicago, Illinois USA

### Abstract

**Objective/Background**—To compare sleep and circadian variability in adults with delayed sleep-wake phase disorder (DSWPD) to healthy controls.

**Patients/Methods**—Forty participants (22 DSWPD, 18 healthy controls) completed a 10-day protocol, consisting of DLMO assessments on two consecutive nights, a five-day study break, followed by two more DLMO assessments. All participants were instructed to sleep within one hour of their self-reported average sleep schedule for the last four days of the study break. We analyzed the participants' wrist actigraphy data during these four days to examine intraindividual variability in sleep timing, duration and efficiency. We also examined shifts in the DLMO from before and after the study break.

**Results and Conclusions**—Under the same conditions, people with DSWPD had significantly more variable wake times and total sleep time than healthy controls ( $p = 0.015$ ). Intraindividual variability in sleep onset time and sleep efficiency was similar between the two groups ( $p = 0.30$ ). The DLMO was relatively stable across the study break, with only 11% of controls but 27% of DSWPDs showed more than a one hour shift in the DLMO. Only in the DSWPD sample was greater sleep variability associated with a larger shift in the DLMO ( $r=0.46$ ,  $p=0.03$ ). These results suggest that intraindividual variability in sleep can be higher in DSWPD versus healthy controls, and this may impact variability in the DLMO. DSWPD patients with higher intraindividual variability in sleep are more likely to have a shifting DLMO, which could impact sleep symptoms and the optimal timing of light and/or melatonin treatment for DSWPD.

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**Corresponding author:** Helen J. Burgess, PhD, Biological Rhythms Research Laboratory, 1645 West Jackson Blvd, Suite 425, Chicago IL 60612, phone 1 312 563 4785, fax 1 312 563 4900, Helen\_J\_Burgess@rush.edu.

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## Keywords

circadian; sleep; light; variability

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## 1.0 Introduction

Delayed sleep-wake phase disorder (DSWPD) is a circadian rhythm sleep disorder. It is characterized by a significant delay in the timing of the major sleep episode, with habitual sleep onset and wake times occurring several hours later than desired socially acceptable times [1]. While people with DSWPD typically complain about not being able to fall asleep and difficulty waking at desired (earlier) times, their sleep duration and architecture is usually normal for age once sleep is initiated [1, 2]. DSWPD is likely due to a multitude of co-occurring factors, including: (1) a longer endogenous circadian period [3], (2) increased sensitivity or exposure to evening light [4], (3) decreased sensitivity or exposure to morning light [1], (4) reduced homeostatic sleep pressure in the evening [5], (5) comorbid features of an insomnia disorder [6], (6) light exposure associated with forced early awakenings causing phase delays [1], (7) a slower rise in evening melatonin levels [7], and (8) partial sleep deprivation which can reduce phase advances to morning light [8]. All these factors can drive the circadian promotion of sleep to later clock times, thus perpetuating and promoting DSWPD [9].

The most reliable measure of central circadian timing in humans is the dim light melatonin onset (DLMO) [10, 11]. Melatonin typically begins to rise in the 2–3 hours before the usual onset of nocturnal sleep [12], but must be measured in dim light as light can suppress melatonin secretion [13]. The assessment of the DLMO in DSWPD is encouraged to improve diagnostic accuracy [1, 14], and to optimize the timing of post-awakening light and afternoon/evening exogenous melatonin treatment of DSWPD [15–18]. Treatment recommendations [19], derived from the light and/or melatonin phase response curves [20, 21], often implicitly assume a stable DLMO in DSWPD [22]. To our knowledge, only one study has assessed the variability of the DLMO in people with DSWPD [23]. The week to week variability in the DLMO was examined in eight DSWPD and eight healthy controls that slept at times of their own choosing. The study found that 6/8 DSWPDs, but only 3/8 healthy controls showed a week to week DLMO shift of one hour or more, suggesting the possibility of increased variability in the DLMO in DSWPD (Figure 2 in [23]).

We recently completed a 10 day protocol in a larger sample of people with DSWPD and healthy controls [24, 25]. All participants completed two DLMO assessments, followed by a five-day study break, and then two more DLMO assessments. All participants were instructed to sleep within one hour of their self-reported average sleep schedule for the last four days of the study break. In this report, we examined the shift in the DLMO from immediately before to immediately after the study break. We also examined sleep timing during the study break, because shifts in sleep timing can shift the DLMO, presumably via associated changes in light exposure [26, 27]. We hypothesized that when DSWPD and healthy controls were assessed under the same conditions, there would be greater sleep and circadian variability in DSWPD as compared to healthy controls.

## 2.0 Materials and Methods

### 2.1 Participants

Data from 41 participants (21–52 years) were derived from two previous studies [24, 25] and included 23 participants with DSWPD and 18 healthy controls. However, a wrist monitor failed in one DSWPD participant, resulting in a final sample of 22 DSWPD and 18 healthy controls (Table 1). All participants selected for analysis were required to have valid DLMOs, and selected healthy controls were required to be  $\leq$  52 years, to match the oldest DSWPD participant. All participants were medication free (including antidepressants and antipsychotics) and based on their responses to screening questionnaires, had no medical disorders (Tasto Health Questionnaire [28]) and were considered low risk for obstructive sleep apnea (Berlin Sleep Apnea Questionnaire [29]), restless legs syndrome (IRLSSG consensus criteria for Restless Legs Syndrome [30]), and psychiatric disorders (Minnesota Multiphasic Personality Inventory-2 [31]). Each DSWPD participant underwent a telephone clinical interview with a board-certified sleep clinician (MP, JW) who confirmed they met the ICSD-2 criteria [32] for delayed sleep phase disorder. These criteria included: (1) a chronic or recurrent complaint of an inability to fall asleep at a desired conventional clock time, (2) an inability to awaken at a desired and socially acceptable time, (3) a delayed but otherwise stable sleep schedule, as verified with at least one week of sleep times recorded on a sleep diary (provided to sleep clinicians prior to telephone interview), (4) normal sleep quality and duration for age when allowed to choose a preferred sleep schedule and (5) sleep disturbance is not better explained by another current sleep disorder, medical, neurological, mental, substance use disorder or medication use. All participants passed a urine drug screen for common drugs of abuse and nicotine, and were not color blind as determined by the Ishihara test. All participants reported moderate caffeine and alcohol use ( $<$ 300 mg/day of caffeine and  $<$ 14 alcoholic drinks/week). All participants had not worked any night shifts in at least two months prior to the study and had not travelled across more than one time zone in the month preceding the study. Non-steroidal anti-inflammatory drugs (NSAIDs) were not permitted throughout the study as they can suppress melatonin [33]. All participants gave written informed consent prior to their participation. All participants expressing interest in treatment were referred for treatment at the end of the study. The study was approved by the Rush University Medical Center Institutional Review Board.

### 2.2 Protocol

Prior to the start of the study protocol, each participant noted their bedtime, estimated sleep onset latency, and wake time for a week with a daily sleep diary. Participants were not required to follow a fixed sleep-wake schedule during this week. From this, each participant's average prestudy sleep onset time (bedtime + sleep onset latency) and wake time was calculated. All participants then participated in a 10-day protocol that consisted of two DLMO assessments, a five-day study break, and two more DLMO assessments. The five-day study break always occurred on a Thursday to Sunday. During the five-day study break, participants were instructed to sleep as desired on the first night, to recover from a two-hour delay in their bedtime the night before, as they sampled saliva in dim light for later determination of the DLMO. Thereafter, on the second, third, fourth and fifth nights of the study break, participants were to instructed to maintain their bedtime and wake times within

a one-hour window ( $\pm 30$  minutes), centered at their average prestudy sleep onset time and average prestudy wake time. This instruction was designed to stabilize their sleep and circadian timing before the DLMO was reassessed after the study break.

All participants wore a wrist actigraphy monitor (30 second epochs, Actiwatch Spectrum, Respironics, Bend, OR) on their non-dominant wrist throughout the 10-day study, and were instructed to press the event marker before and after sleep each day. To reduce study burden, participants were not required to complete sleep diaries during the study break.

The DLMOs collected immediately the evening before and evening after the study break were assessed from half-hourly saliva samples collected with Salivettes (Sarstedt, Newton, NC). The DLMOs were either collected in the laboratory in dim light ( $<5$  lux) or at home ( $<50$  lux). Others have shown that even in dark adapted individuals, minimal melatonin suppression occurs at light intensities  $<50$  lux [34], and we have previously shown that saliva samples collected in  $<50$  lux yield accurate DLMOs [24, 25]. All saliva samples were frozen at  $-20$  °C after centrifuging and radioimmunoassayed (ALPCO, Inc., Macedon, NY, USA).

### 2.3 Data Analysis

The wrist actigraphy data was analyzed with the Actiware 6.0.7 program (Respironics, Bend, OR). The setting of nightly rest intervals for analysis was guided by the event markers, light data and activity levels [35]. The night-by-night actigraphic estimates of sleep onset time (clock time of the first epoch scored as sleep in each rest interval), wake time (clock time of the last epoch scored as sleep in each rest interval), total sleep time (number of minutes scored as sleep in each rest interval) and sleep efficiency (proportion of time from sleep onset to wake in each rest interval, scored as sleep, expressed as a percentage) were extracted. Due to the absence of sleep diary data, and an accurate “tried to fall asleep” time, sleep onset latency was not estimated. A DLMO was calculated for each phase assessment and defined as the clock time (with linear interpolation) when the melatonin concentration exceeded the mean of three low consecutive daytime values plus twice the standard deviation of these points [36]. This low threshold more closely tracks the initial rise of melatonin [37].

The baseline characteristics of the healthy controls and participants with DSWPD were compared with independent t-tests for continuous variables and Chi-squares for categorical variables. Global averages in sleep measures were compared with a MANOVA. Night-to-night variability in the sleep variables across nights 2–5 were assessed with the root mean squared successive difference (RMSSD) [38]. Statistical significance for all tests was determined at  $p < 0.05$  using two-tailed statistical tests unless otherwise stated.

## 3.0 Results

### 3.1 Baseline characteristics

The baseline characteristics of the healthy control and DSWPD participants are shown in Table 1. There were no group differences in sex, age, body mass index, race, employment status, or number of morning commitments. The average morningness-eveningness score

derived from the Morningness-Eveningness Questionnaire [39] was significantly different between groups, revealing as expected, more eveningness in the DSWPD sample. Similarly, before the study started, the DSWPD participants reported falling asleep on average about three hours later and waking on average about two hours later than the controls. While not statistically significant, the DSWPD participants reported on average one hour less sleep per night than the healthy controls. Lastly, before the study break, the average DLMO of the DSWPD participants was two hours later than the average DLMO in the healthy controls.

### 3.2 Sleep

Sleep variables were first averaged across the last four nights of the study break to examine global group differences. As expected, the DSWPD participants had on average a significantly later sleep onset time ( $02:20 \pm 1.2$  vs.  $00:10 \pm 1.0$ ,  $p < 0.001$ ) and wake time ( $9:42 \pm 1.5$  vs.  $7:53 \pm 1.3$ ,  $p < 0.001$ ), than the healthy controls. There was no difference in total sleep time between the DSWPD participants and healthy controls ( $404.1 \pm 50.6$  vs.  $425.6 \pm 51.7$ ,  $p = 0.19$ ). Sleep efficiency, as calculated after sleep onset, was on average equally good between groups ( $91.9 \pm 3.4$  vs.  $91.9 \pm 3.0$ ,  $p = 0.97$ ).

The effects of weekend (Friday and Saturday nights) and weekdays (Sunday and Monday nights) on sleep variables in both groups were also examined. As expected, there was a group main effect by which DSWPD participants slept later than healthy controls ( $p < 0.001$ ), and a weekend effect by which both groups had a significantly later sleep onset and wake time on weekend versus weekdays ( $p = 0.03$ ). However, there was no group by weekend effect ( $p = 0.44$ ). On average, the DSWPDs went to sleep 30.2 minutes later and woke 36.8 minutes later on the weekend, whereas the healthy controls only went to sleep 7.7 minutes later and woke 27.2 minutes later on the weekend. There were no weekday versus weekend effects on total sleep time or sleep efficiency in either group (all  $p$ s  $> 0.37$ ).

The variability in the sleep variables during the study break are shown in Figures 1–4. The RMSSD data were first log transformed, before they were compared between groups, but the untransformed RMSSD data are reported. This analysis revealed that the DSWPD participants had significantly more variable wake times ( $1.31 \pm 1.00$  vs.  $0.72 \pm 0.56$ ,  $p = 0.015$ ) and significantly more variable total sleep time ( $80.62 \pm 50.83$  vs.  $46.20 \pm 30.28$ ,  $p = 0.012$ ) than healthy controls. However, variability in sleep onset time ( $1.09 \pm 0.76$  vs.  $0.84 \pm 0.53$ ,  $p = 0.30$ ) and sleep efficiency ( $3.13 \pm 1.73$  vs.  $3.56 \pm 2.71$ ,  $p = 0.93$ ) was similar between groups. There were no weekday versus weekend difference in RMSSD values for each sleep variable in either group (all  $p$ s  $> 0.45$ ). There was also no significant association between RMSSD values for each sleep variable and the number of morning commitments per week (all  $p$ s  $> 0.34$ ).

### 3.3 Circadian Phase

There was no sex difference in the DLMO measured before and after the study break ( $p > 0.64$ ). The phase angle difference between the average sleep onset time during the last 4 days of the study break and the DLMO assessed immediately after the study break, did not differ between the DSWPDs and healthy controls ( $3.0 \pm 1.0$  h vs.  $3.4 \pm 1.3$  h,  $p = 0.35$ , respectively). The DLMOs before and after the study break are shown in Figure 5. As

expected, the DSWPDs on average had later DLMOs than the healthy controls ( $p < 0.001$ ), but overall there was not a significant shift in the DLMO ( $p = 0.42$ ). There was a time by group interaction trend by which the DLMO delayed over the study break by average of 8.6 minutes in the DSWPD participants, whereas the DLMO advanced in the healthy controls by an average of 22.0 minutes ( $p = 0.071$ ), although the magnitude of these changes in the DLMO were small. As hypothesized, only two healthy controls but six DSWPD participants had more than a one-hour shift in their DLMOs from before to after the study break, but this did not reach statistical significance (one-tailed Fisher's exact test  $p = 0.19$ ). Furthermore, no healthy controls had more than a 1.5-hour shift in their DLMO while three DSWPD participants did, but this also did not reach statistical significance (one-tailed Fisher's exact test  $p = 0.16$ ). The only sleep variability parameter that significantly correlated with the shift in the DLMO was sleep onset variability, which was positively associated with a larger shift in the DLMO ( $r = 0.46$ ,  $p = 0.03$ ), but only in the DSWPD participants.

## 4.0 Discussion

In this study, we examined sleep and circadian variability in people with DSWPD as compared to controls. All participants received the same instruction: to maintain their sleep schedule for four days within a one-hour window centered around their prestudy average sleep onset and wake times. We found increased sleep and circadian variability in DSWPD participants versus healthy controls even with this instructed stabilization of sleep schedule. Specifically, DSWPD participants were more variable in their wake times and total sleep time than healthy controls. These differences are consistent with the observation that people with DSWPD often wake later when their social schedule permits, but force themselves to wake up earlier, to meet morning social obligations [22]. This behavior would be expected to lead to increased variability in wake times, and consequently increased variability in total sleep time in DSWPD. Of note, DSWPD participants did not show increased variability in sleep onset times or sleep efficiency (after sleep onset) as compared to healthy controls, consistent with the notion that their delayed sleep onset is relatively stable [1] and their sleep, once initiated, is usually normal for age [1, 2]. Indeed, both the DSWPDs and healthy controls mostly had high sleep efficiencies after initially falling asleep. We also found a higher prevalence of a shift in the DLMO from before to after the study break in participants with DSWPD than in healthy controls, consistent with higher week to week DLMO variability reported in an earlier study [23]. Overall almost a third of DSWPD participants showed a shift in the DLMO of more than one hour during the study break despite an instruction to maintain a stable sleep schedule. However, the shift in the DLMO was only positively correlated with variability in sleep onset (and not wake time) and only in the DSWPD participants. It is not clear why this is the case, but we note that due to our instruction to all participants to stabilize their sleep schedule, the variability in sleep and circadian timing observed in this study is likely significantly less than what would naturally occur in the field.

While we did not measure any clinical outcomes in this study, the increased sleep variability in DSWPD could be clinically significant, as others have reported that increased sleep variability is associated with worse health outcomes, including depression [40], insomnia [41], obesity [42] and insulin resistance [43]. Future studies could examine the relationship

between sleep variability in DSWPD and clinical outcomes. Additionally, it is possible that the health benefits of post-awakening light and/or afternoon/evening melatonin for DSWPD extend beyond eliciting a circadian phase advance (and the associated increase in sleep duration), to also enabling a more stable sleep schedule and reduced sleep variability. Currently, the collection of at least a week of sleep diary and/or wrist actigraphy monitoring to “demonstrate a delay in the timing of the habitual sleep period” is suggested as part of the diagnosis of DSWPD [1]. When considering treatment, we encourage clinicians to also examine the variability in sleep timing, as this is likely to influence the variability in the DLMO. A DSWPD patient with higher sleep variability is more likely to have a shifting, rather than stable DLMO. Thus, if the DLMO is used to guide the timing of post-awakening light and/or afternoon/evening melatonin treatment [19–21], treatment may be optimized if sleep timing variability is also considered. However, we note that the additional consideration of sleep variability in treating DSWPD requires more examination.

We observed a range in the timing of the DLMO in our sample of DSWPD participants (Figure 5), who underwent a telephone clinical interview with a board-certified sleep clinician who confirmed that they met the ICSD-2 criteria for DSWPD [32]. The range in DLMO highlights the importance of measuring the DLMO to assist in the diagnosis of DSWPD, which is increasingly encouraged [1, 14]. One DSWPD participant had a DLMO as early as 19:37. This participant was employed fulltime and reported an average bedtime 01:00 and wake time of 7:00. If the clinician had known the timing of his DLMO, they would have suspected insomnia rather than DSPD. This individual highlights the usefulness of the DLMO in diagnosing DSWPD.

In this study the DSWPD participants did not significantly differ from the sample of healthy controls in a number of important factors, including age, sex, body mass index, race, employment status, and number of morning commitments. These similarities between the two groups increase our confidence that the differences in sleep and circadian variability were due to DSWPD, and not some external related factor. Nonetheless, only 25% of our samples were employed full time and on average the healthy controls and DSWPD participants reported only 2–3 morning commitments per week (Table 1). The variability in sleep and circadian timing could be expected to be greater in DSWPD patients who work full time or have more morning commitments. Notably, we assessed objective sleep variability with wrist actigraphy and did not rely on subjective sleep reports, which can be less accurate. Nonetheless, we acknowledge several weaknesses in our study, including that we were not able to assess sleep across an entire seven-day week (although we did assess some weekdays and weekends). Also, we assessed sleep after a night where participants could sleep whenever they wanted to, in order to recover from some study-induced sleep deprivation, and this could have potentially influenced the sleep and circadian variability during the study break. However, both the DSWPD participants and healthy controls were assessed in the same conditions, increasing the likelihood that DSWPD is indeed associated with greater sleep and circadian variability. Additionally, as prestudy sleep was assessed with a sleep diary and not wrist actigraphy, it remains possible that participants may have misrepresented their sleep before the study began, thereby making it more difficult for them to follow the fixed sleep schedule during the study break. However, there was no incentive for participants to misrepresent their sleep. We also note that while our sample of 22

DSWPD participants is the largest sample to date to examine sleep and circadian variability in DSWPD, this relatively small sample size may limit the statistical power and generalizability of our findings. We therefore encourage other researchers with wrist actigraphy or multiple DLMO assessments in larger samples of DSWPD participants to examine their data with a focus on sleep and circadian variability. In conclusion, the results of this study suggest increased sleep and circadian variability in DSWPD as compared to healthy controls. Increased sleep variability is likely to lead to increased variability in the DLMO, and this should be taken into consideration when timing light and/or melatonin treatments relative to the DLMO to treat DSWPD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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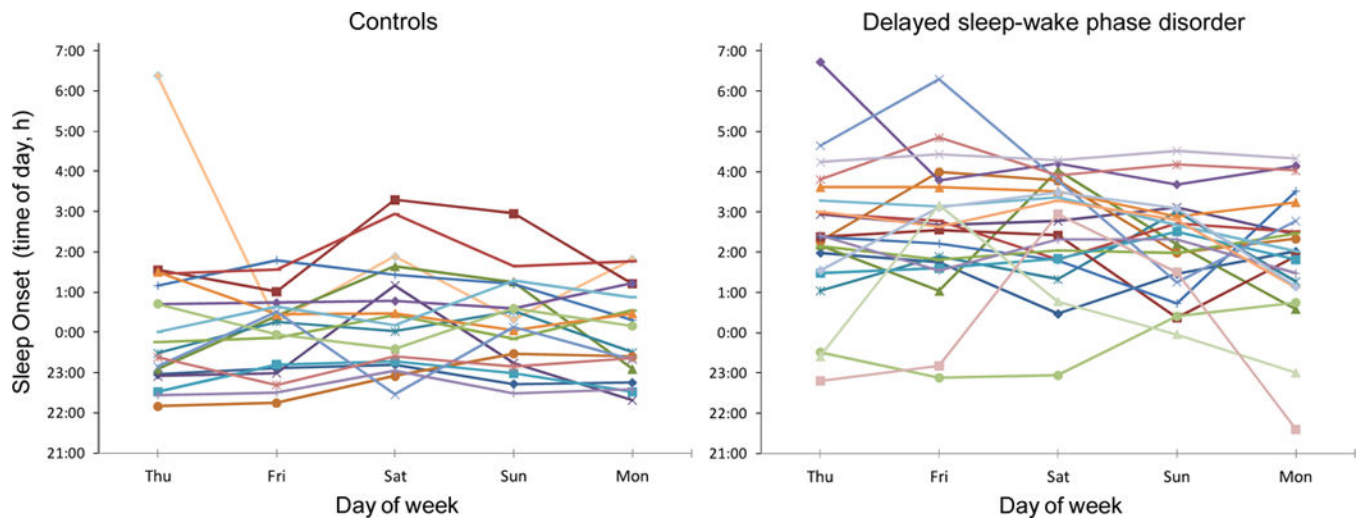
- Delayed Sleep Wake Phase Disorder is associated with greater sleep variability
- Greater sleep variability may contribute to greater variability in circadian timing
- When treating Delayed Sleep Wake Phase Disorder consider sleep variability

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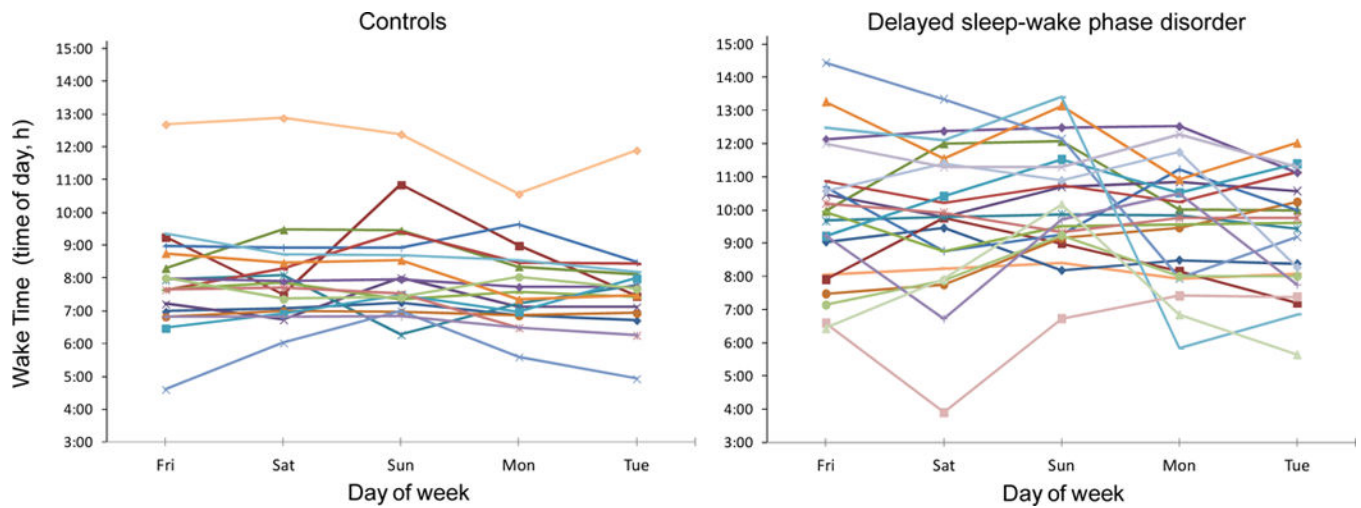
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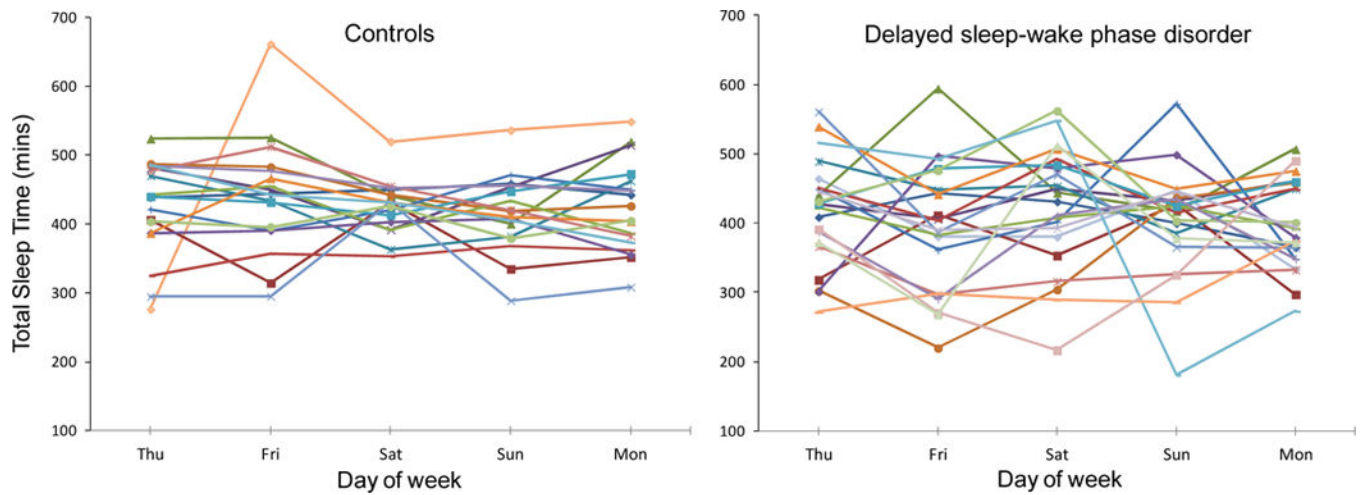


**Figure 1.**

Sleep onset times during the study break in healthy controls (left) and participants with delayed sleep-wake phase disorder (DSWPD, right). Participants were permitted to sleep at any time on Thursday night to recover from study-induced sleep deprivation. After that, on Friday through Monday nights, participants were instructed to sleep within 30 minutes of their average prestudy sleep onset and wake times. The variability in sleep onset on Friday through Monday was not significantly different between the DSWPD participants and healthy controls ( $p=0.30$ ). The same symbols and colors are used for the same participants in the other figures.

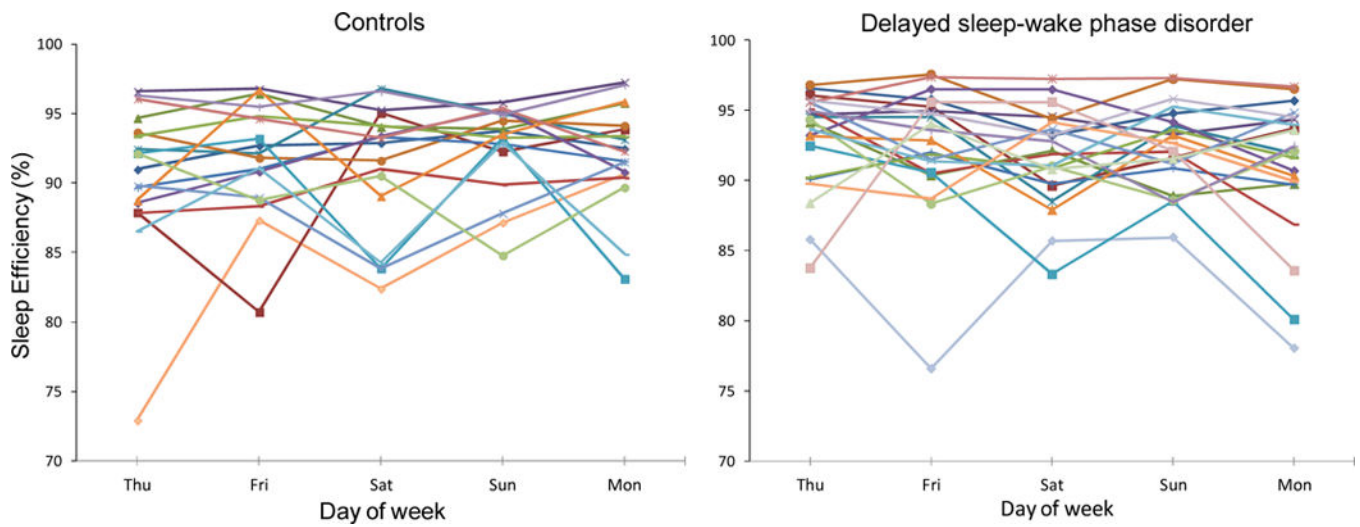


**Figure 2.** Wake times during the study break in healthy controls (left) and participants with delayed sleep-wake phase disorder (DSWPD, right). Participants were permitted to wake at any time on Friday morning to recover from study-induced sleep deprivation. After that, on Saturday through Tuesday mornings, participants were instructed to sleep within 30 minutes of their average prestudy sleep onset and wake times. The variability in wake time on Saturday through Tuesday was significantly higher in the DSWPD participants versus healthy controls ( $p=0.015$ ). The same symbols and colors are used for the same participants in the other figures.

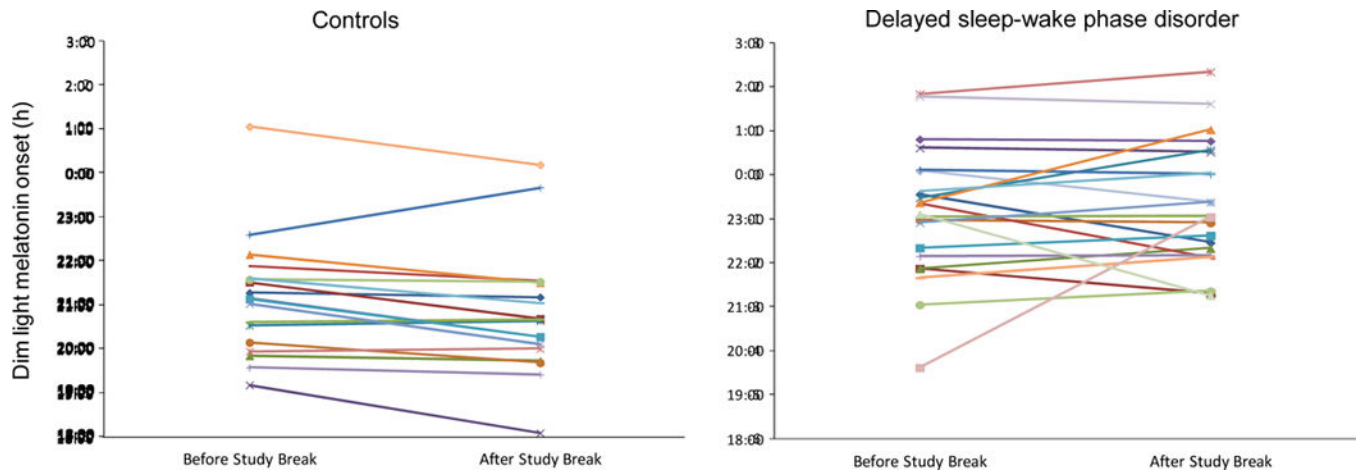


**Figure 3.**

Total sleep time during the study break in healthy controls (left) and participants with delayed sleep-wake phase disorder (DSWPD, right). Participants were permitted to sleep at any time on Thursday night to recover from study-induced sleep deprivation. After that, on Friday through Monday nights, participants were instructed to sleep within 30 minutes of their average prestudy sleep onset and wake times. The variability in total sleep time on Friday through Monday was significantly higher in the DSWPD participants versus healthy controls ( $p=0.012$ ). The same symbols and colors are used for the same participants in the other figures.



**Figure 4.** Sleep efficiency (after sleep onset) during the study break in healthy controls (left) and participants with delayed sleep-wake phase disorder (DSWPD, right). Participants were permitted to sleep at any time on Thursday night to recover from study-induced sleep deprivation. After that, on Friday through Monday nights, participants were instructed to sleep within 30 minutes of their average prestudy sleep onset and wake times. The variability in sleep efficiency on Friday through Monday was not significantly different between the DSWPD participants versus healthy controls ( $p=0.93$ ). The same symbols and colors are used for the same participants in the other figures.



**Figure 5.** The clock time of the dim light melatonin onsets (DLMOs) measured immediately before and after the 5 day study break in healthy controls (left) and participants with delayed sleep-wake phase disorder (DSWPD, right). Participants were permitted to sleep at any time on the first night of the study break, but for the remaining 4 nights participants were instructed to sleep within 30 minutes of their average prestudy sleep onset and wake times. Only 2 healthy controls but 6 DSWPD participants had more than a 1 hour shift in the DLMO. The same symbols and colors are used for the same participants in the other figures.



**Table 1**

Baseline characteristics of the healthy control and delayed sleep-wake phase disorder participants.

	<b>Controls Mean (S.D.)</b>	<b>Delayed Sleep-Wake Phase Disorder Mean (S.D.)</b>	<b>Group difference</b>
Sex	9 M, 9 F	13 M, 9 F	p=0.57
Age (y)	30.8 (7.3)	28.0 (7.2)	p=0.16
Body mass index (kg/m <sup>2</sup> )	24.2 (3.1)	23.4 (3.7)	p=0.48
Race (White, Black, Asian, other)	12 W, 3 B, 1 A, 2 O	15 W, 0 B, 4 A, 3 O	p=0.17
Employment (FT, PT, not working)	6 FT, 8 PT, 4 NW	4 FT, 8 PT, 10 NW	p=0.27
Morning commitments (per week)	2.8 (2.0)	1.9 (2.3)	p=0.17
Morningness-eveningness score	50.4 (9.4)	35.7 (6.8)	<b>p&lt;0.001</b>
Average prestudy sleep onset (h:mm)	23:40 (0.94)	02:44 (2.4)	<b>p&lt;0.001</b>
Average prestudy wake time (h:mm)	07:47 (0.6)	09:49 (1.4)	<b>p&lt;0.001</b>
Average prestudy sleep duration (h)	8.1 (0.6)	7.1 (2.9)	p=0.12
DLMO before study break (h:mm)	21:09 (1.3)	23:09 (1.5)	<b>p&lt;0.001</b>

FT = fulltime employment, PT = part-time employment.

Morning commitments were defined as regular commitments occurring before noon.

Bold highlights the group differences that reached statistical significance.