Sleep Research Society®

Article Navigation

EDITOR'S
CHOICE

Habitual light exposure relative to circadian timing in delayed sleep-wake phase disorder FREE

John Wilson, IV, Kathryn J Reid, Rosemary I Braun, Sabra M Abbott, Phyllis C Zee

Sleep, Volume 41, Issue 11, November 2018, zsy166, https://doi.org/10.1093/sleep/zsy166
Published: 23 August 2018 **Article history ▾**

PDF Split View Cite Permissions Share ▾

Abstract

Study Objectives

To compare melatonin timing, a well-validated marker for endogenous circadian phase, and habitual light-exposure patterns in adults with delayed sleep-wake phase disorder (DSWPD) and intermediate chronotype controls.

Methods

Twelve individuals with DSWPD (five females, mean age: 31.1) and 12 age-matched controls (six females, mean age: 33.6) underwent a minimum of 7 days of light and activity monitoring followed by an inpatient hospital stay, where blood was taken to assess melatonin timing (calculated as dim light melatonin onset—DLMO). Habitual light-exposure patterns were then compared with a human phase-response curve (PRC) to light.

Results

Relative to clock time, individuals with DSWPD had a later light-exposure pattern compared with controls, but their light-exposure pattern was earlier relative to DLMO. According to the human PRC to light, individuals with DSWPD had less daily advancing light exposure compared with controls. The primary difference was seen in the late portion of the advancing window, in which individuals with DSWPD were exposed to fewer pulses of light of equivalent duration and intensity compared with controls.

Conclusions

Diminished advancing light exposure may play a role in the development and perpetuation of delayed sleep-wake timing in individuals with DSWPD. Enhancing light exposure during the later portion of the advancing window represents an innovative and complementary strategy that has the potential to improve the effectiveness of bright light therapy in DSWPD.

circadian rhythm disorders, light therapy, actigraphy

Statement of Significance

To the best of our knowledge, this is the first study to examine the relationship between habitual light exposure and endogenous circadian phase in individuals with delayed sleep-wake phase disorder (DSWPD) and controls. The diminished light exposure in the late advancing window found in this study is of particular interest because future research might assess whether light treatments targeting the late advancing window result in improved clinical responses compared with existing treatment methods in individuals with DSWPD. Targeting light therapy at specific “circadian treatment windows” can help personalize therapy and improve treatment outcomes.

Introduction

The rotation of the Earth causes daily fluctuations in the environment which have shaped various adaptations in humans and other organisms [1]. Many physiological processes oscillate with rhythms that have a period (cycle length) of approximately 24 hr, known as circadian rhythms. Circadian period length (i.e. the time interval needed to complete one full circadian cycle) in humans averages slightly longer than 24 hr [2]. This results in a tendency for circadian timing to drift later each day, so in most individuals regular adjustment via environmental time cues is necessary to maintain stable coordination between environmental and social/activity cycles [3, 4]. The most powerful circadian entraining stimulus is light. Light exposure during the biological evening shifts the timing of the circadian system towards later hours, whereas exposure during the biological morning shifts circadian timing earlier [5]. The relationship of light exposure to shifts in timing of the circadian system has been delineated in the human phase-response curve (PRC) to light [6]. Melatonin is one biomarker used to measure the timing of circadian rhythms. It is a hormone secreted predominantly at night, rising on average 2–3 hr before habitual sleep onset. The time of onset of this rise is referred to as the dim light melatonin onset (DLMO) [7].

Circadian rhythm sleep-wake disorders (CRSWD) are sleep disorders that arise from a misalignment of the endogenous timing of the circadian system with the external 24 hr environment [8]. Among the CRSWDs, it has been suggested that between 7 and 16 per cent of the population is affected by delayed sleep-wake phase disorder (DSWPD), including 10 per cent of those individuals presenting to sleep clinics with the complaint of insomnia [8–10]. DSWPD is a condition characterized by a delayed timing of sleep onset compared with social convention resulting in impaired daytime functioning [8, 11, 12]. Individuals with DSWPD generally exhibit a stable delay in the timing of the circadian system, but the etiology of this delay remains uncertain [8, 11, 13-19].

Only two studies have attempted to characterize habitual light-exposure patterns in patients with DSWPD. Auger and colleagues compared light exposure in 16 adolescents with DSWPD and 22 age-matched controls [20]. Compared with controls, patients with DSWPD were exposed to higher light levels during the evening and lower levels in the morning, but this was primarily related to differences in sleep timing. When light exposure was analyzed in relation to sleep-wake timing rather than clock time, patients with DSWPD received less light in a 9 hr interval prior to sleep onset, and no differences were found during the 9 hr interval after sleep offset. Similar results showing higher light exposure during the night (2:00–4:00) and lower light exposure in the morning (8:00–11:00) in patients with DSWPD compared with age and sex-matched controls were reported in another larger study [21]. In addition, light levels were higher 22 hr after habitual wake time in the DSWPD group, which typically occurred during sleep. Both studies indicate that although there are differences in light exposure between the two groups with respect to clock time, those differences may not be as pronounced with respect to circadian time. However, a limitation of both studies was that sleep timing, which may not accurately reflect the phase of circadian rhythms, was used to align light timing.

The aim of the current study was to assess the relationship between the timing of melatonin, a well-validated physiological measure of endogenous circadian phase, and habitual light-exposure patterns in participants with DSWPD and intermediate chronotype controls. We hypothesized that participants with DSWPD would have a later light-exposure pattern relative to DLMO (or inversely, that DLMO would be earlier relative to the light-exposure pattern) compared with controls. All else being equal, this would delay the timing of the sleep-wake rhythm based on the human PRC to light. Further knowledge of the habitual light-exposure patterns of individuals with DSWPD in relation to their internal biological time may help understand the etiology of the disorder and inform future refinements in treatment protocols.

Methods

Participants

This study examined 12 healthy adults with DSWPD (ages 21–62) and 12 healthy age-matched controls (ages 21–65). Participants were considered to have DSWPD if they met the International Classification of Sleep Disorders (ICSD-2) criteria for DSWPD as determined by a board-certified

sleep physician [22]. Control participants had a stable sleep/wake schedule with sleep onset no later than 12:30 am, an intermediate score (42–58) on the Horne-Östberg Questionnaire, and no history of sleep disorders.

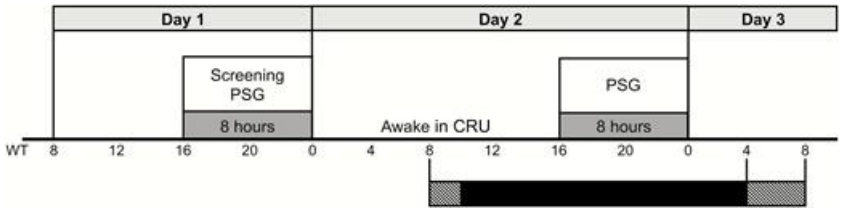
All participants were required to have a stable habitual sleep/wake schedule (i.e. a pattern that is not drifting earlier or later each day) verified by wrist actigraphy. Exclusion criteria for all participants included diagnosis of a sleep disorder (other than DSWPD) as assessed by polysomnography, a history of cognitive or neurological conditions, serious medical illness, psychiatric disorder or substance abuse problems as determined by clinical interview using the Diagnostic and Statistical Manual (DSM-IV) and Structured Clinical Interview for DSM (SCID-I), use of psychoactive medications, hypnotics, or any medication influencing melatonin levels, smoking, shift work, daily caffeine intake greater than the equivalent of four cups of coffee per day, or pregnancy or desire to become pregnant during the study period.

Procedures

Participants were recruited between January 2004 and November 2007 through printed and online advertisements. Advertisements solicited people with normal sleep times and those with an "extreme evening preference" or who considered themselves a "night owl." Participants were required to give written informed consent prior to participation and all study procedures were approved by the Northwestern University Institutional Review Board. During the initial screening, participants were interviewed by a board-certified sleep physician and a clinical psychologist to determine eligibility and DSWPD status. They completed questionnaires (including the Horne–Östberg questionnaire, Pittsburg Sleep Quality Index [PSQI], Beck Depression Index [BDI], and Epworth Sleepiness Scale [ESS]), recorded a sleep diary, and wore an Actiwatch-L (Mini Mitter Co. Inc, Bend, OR) device for a minimum of 2 weeks to assess their habitual rest-activity patterns. Eligible participants wore the Actiwatch-L and kept a sleep diary again for at least a week prior to their stay at the Clinical Research Unit (CRU) at Northwestern Memorial Hospital. During this recording interval, participants were asked to maintain their habitual (i.e. screening actigraphy) sleep pattern (±1 hr). Participants did not travel across time zones 1 month preceding the study and did not travel during the study.

Participants were admitted to the CRU approximately 3 hr after their habitual wake time (Figure 1). They were then placed on a modified constant routine protocol consisting of 60 hr of bed rest with 8 hr sleep periods beginning at habitual bedtimes. Light levels were <10 lux during waking hours and <3 lux during sleep. Six hours after waking on day 2, an indwelling venous catheter was placed. Blood samples were collected over 24 hr. The sampling frequency was hourly for the first 2 and last 4 hr, with collection every 30 min in the intervening period. For the duration of sampling while awake, participants remained in a semirecumbent posture under dim light with isocaloric snacks every 2 hr.

Figure 1.



View large Download slide

Study protocol for the inpatient visit. For 7 days immediately prior to admission to the CRU, participants were instructed to wear an actiwatch and keep a sleep log while maintaining their habitual sleep schedule ± 1 hr. On admission, participants were placed on a modified constant routine protocol consisting of bed rest with 8 hr sleep periods beginning at habitual bed times. During the first night, a screening PSG was performed to rule out sleep disorders other than DSWPD. Starting 8 hr after wake on day 2, blood was drawn through an indwelling catheter for 24 hr to assess melatonin levels. Blood was drawn every hour for the first 2 and last 4 hr of sampling, and every 30 min in the intervening time. This is shown by the shaded box at the bottom of the figure. WT = time since wake; PSG = polysomnography.

Wrist actigraphy

Light and activity levels were determined at the wrist using the AW-L Actiwatch (Mini Mitter Co. Inc., Bend, OR). Participants were instructed to wear the watch on their nondominant wrist and avoid covering the watch with their clothing. Sleep logs included information about daily bed times, wake times, estimated sleep onset and offset, naps, and periods where the participant was not wearing the watch. The screening actigraphy recording interval was 14 days, and the pre-CRU recording interval was at least 7 days.

Melatonin

Plasma melatonin levels were measured from blood samples using a commercially available radioimmunoassay from IBL International (Catalog No. RE29301). The standard range of sensitivity for this assay is from 3 to 300 pg/mL.

Measures

Light and activity

Data from the week prior to the CRU admission were prepared for this analysis in Actiware 5.59 (Philips/Respironics) as described previously [21, 23]. Periods of 30 min or greater with no activity and high light levels during wake were excluded as off wrist. For a day to be included in the analysis, it could not have more than 2 hr of excluded data. Each participant was required to have a minimum of 4 days of valid light data.

Sleep start, sleep end, sleep midpoint, and sleep duration were calculated using Actiware 5.59 software. Rest intervals were set using the self-reported bed times and wake times as recorded in the sleep diary. Sleep start was defined as the first 10 min period in which no more than one epoch was scored as "mobile." Sleep end was defined as the last 10 min period in which no more than one epoch was scored as "immobile." Sleep midpoint was defined as the half-way point between sleep start and sleep end for each episode of sleep. Sleep duration was defined as the amount of time between sleep start and sleep end.

Melatonin

DLMO 20% ($DLMO_{20}$) was calculated using previously described methods. This measure was chosen due to its high stability over time [7].

Phase angles

Two phase angles were calculated as follows: the difference between average sleep start and $DLMO_{20}$ (SS-$DLMO_{20}$) and the difference between average sleep end and $DLMO_{20}$ (SE-$DLMO_{20}$). These were chosen for comparison to previous studies and for their relevance to morning and evening light exposure. In this analysis, we will use "phase angle" to refer to SS-$DLMO_{20}$.

Light and activity analysis

Light and activity data were down-sampled or "binned" to a 1 hr resolution combining all valid days of data for each person. This was done with respect to clock time and melatonin time (MT; relative to $DLMO_{20}$). Light exposure recorded during sleep periods was excluded from all analysis (counted as 0). The amount of time above a threshold of 1000 lux (TAT_{1000}) was calculated as the number of minutes of recorded light exposure above that threshold divided by the number of days of light recording in the analysis. The mean timing of light above 500 lux ($MLiT_{500}$) was calculated as the mean time (hh:mm) of all light-exposure data, combined across each day included in the analysis, above a threshold of 500 lux (with reference to previously described methods) [24].

The advancing and delaying portions of the PRC to light were estimated relative to $DLMO_{20}$ based on the results of St. Hilaire and colleagues [25]. This PRC was chosen because the 1 hr light pulse was felt to be the most appropriate comparison to real world light exposure among the available PRCs. Light between 7 hr after $DLMO_{20}$ (MT 7) and 22 hr after $DLMO_{20}$ (MT 22) was considered advancing, whereas light between 22 hr after $DLMO_{20}$ (MT 22) and 7 hr after $DLMO_{20}$ (MT 7) was considered delaying. The advancing portion of the PRC was further broken down into three nonoverlapping sequential 5 hr subintervals noted as A1, A2, and A3 (respectively).

Light was also quantified as "pulses," defined as intervals of time where light intensity was above a threshold of 200 lux. A threshold of 200 lux was chosen because it approximates the intensity of room light and 33 per cent of daily light exposure is of equal or higher intensity in this sample. Interruptions, i.e. light levels of less than 200 lux within a pulse, of 8 min (four consecutive 2 min bins) or less were not included. At least 75 per cent of the duration of each pulse was required to be light above threshold. We reported several variables characterizing the light-exposure pulses within each interval of our analysis. These include the number of pulses on average each day (# of Pulses), the average length of those pulses (Pulse Length), and the average intensity of light exposure within each pulse (Pulse Intensity). We also reported Total Pulse Time, which is the average number of pulses in each interval per day multiplied by the average length of those pulses (# of Pulses × Pulse Length). For key results at a threshold

of 200 lux, we also examined a range of thresholds between 20 and 1000 lux (multiples of 20) and reported the range of thresholds where the result was statistically significant. Unless otherwise noted, all results reflect a threshold of 200 lux.

Statistical analysis

Demographics and sleep characteristics were compared between the two groups using Fisher's exact test for categorical variables and two-sample *t*-tests for continuous variables, as appropriate. Summary statistics (means and standard deviations) are presented for actigraphy variables (sleep start, sleep midpoint, sleep end, and sleep duration) and variables related to pulses of light exposure (number of pulses, length of pulses, total pulse time, and pulse intensity). Means for these variables were calculated by averaging the daily values for each participant before determining group averages. Standard deviations were also calculated using daily values for each participant before determining group averages, and as such they represent a measure of day-to-day variability. For other variables not mentioned, standard deviations are not calculated using daily values for each participant and instead represent variability among participants in each group.

Generalized estimating equations (GEE) for repeated measures were used to model log(lux + 1) and activity as a third-order polynomial in time across all modeling situations. An exchangeable within-subject covariance matrix was estimated to account for the possible correlation between outcome measurements from the same subject, and robust standard errors of the model parameters were computed using the methods of Diggle and colleagues, which yield consistent estimates even when the within-subject covariance matrix is misspecified [26]. An interaction term between the time polynomial and the group (DSWPD/control) was used to model differences in light and/or activity over time in the two groups. Significance of the interaction between the group and any of the polynomial terms was assessed using an *F*-test. A Bonferroni correction was applied to adjust for the number of models considered within each group of analyses.

Light and activity were compared between the DSWPD/control groups across two different time variables (clock time and relative to $DLMO_{20}$) over 24 hr. Light exposure during the 15 hr advancing interval, the three 5 hr subintervals, and the delay interval was compared between the DSWPD/control groups. Season was considered for all of the above sets of comparisons, but because it did not account for a significant amount of variance it was ultimately removed from the analysis.

A Weibull distribution modeling approach was used to provide a method of estimating the window for advancing light exposure without using DLMO, which may not be accessible in a clinic setting. The interval between $DLMO_{20}$ and sleep midpoint was modeled as a Weibull distribution using R package `fitdistrplus` [27]. Maximum likelihood estimation from $N = 24$ observations was used to obtain the shape and scale parameters, respectively. Diagnostic quantile-quantile (qq) and probability-probability (pp) plots were made, followed by Cramer–von Mises and Anderson–Darling statistics (as described previously) to assess the goodness of fit [28]. Quantiles of the resulting Weibull model were then used to obtain estimates of the proportion of individuals who have an interval between $DLMO_{20}$ and sleep midpoint less than or equal to 10:00.

Results

Demographics and sleep characteristics

Table 1 describes demographic information and sleep characteristics for all participants. There were no significant differences between the DSWPD and control groups for age, sex, number of days included in the analysis, season, or work status. Sleep start, sleep end, and sleep midpoint were all significantly later in the DSWPD group compared with the control group ($p < 0.001$). Sleep duration was not significantly different between groups.

Table 1.

Demographics and sleep characteristics for DSWPD/control groups

	DSWPD (*n* = 12)	Controls (*n* = 12)	*P*
Mean age (year)	31.1 (12.6)	33.6 (15.5)	0.67
Sex (F, M)	7 F, 5 M	6F, 6M	1
# days in analysis	8.0 (3.2)	7.6 (1.1)	0.67
Season (SS, FW)	7 SS, 5 FW	8 SS, 4 FW	1
Work status (FT, PT, NW)	5 FT, 2 PT, 5 NW	5 FT, 1 PT, 6 NW	1
Questionnaires			
Pittsburgh Sleep Quality Index	6.83 (2.37)	3.08 (3.42)	0.005
Beck Depression Inventory	8.0 (6.09)	1.83 (3.83)	0.007
Epworth Sleepiness Scale	8.09 (4.74)	5.82 (3.12)	0.2
Horne–Östberg score	28.3 (5.56)	51.83 (5.29)	<0.001
Sleep			
Sleep Start (hh:mm)	3:26 (0:50)	23:55 (0:47)	<0.001
Sleep Midpoint (hh:mm)	7:23 (0:56)	3:44 (0:41)	<0.001
Sleep End (hh:mm)	11:21 (0:43)	7:33 (0:55)	<0.001
Sleep Duration (hh:mm)	7:54 (1:00)	7:38 (0:58)	0.54
Melatonin			
$DLMO_{20}$ (hh:mm)	00:18 (1:21)	20:03 (0:59)	<0.001
Light			
$MLiT_{500}$ (hh:mm)	15:00 (1:02)	13:13 (0:44)	<0.001
TAT_{1000} (min)	42.17 (33.34)	86.58 (99.64)	0.16
Phase angles			
SS-$DLMO_{20}$ (hh:mm)	3:08 (1:26)	3:51 (1:07)	0.18
SE-$DLMO_{20}$ (hh:mm)	11:03 (1:39)	10:36 (3:22)	0.69

Standard deviations are represented in parentheses.

DSWPD = delayed sleep-wake phase disorder; F/M = female, male; SS/FW = spring/summer, fall/winter; FT/PT/NW = full time, part time, not working; $DLMO_{20}$ = dim light melatonin onset 20%; $MLiT_{500}$ = mean time of light above 500 lux; TAT_{1000} = mean time above a threshold of 1000 lux per day; SS-$DLMO_{20}$/SE-$DLMO_{20}$ = phase angle between sleep start/sleep end and $DLMO_{20}$; (hh:mm) = hours:minutes.

View Large

Data from the PSQI showed that the DSWPD group had significantly poorer sleep quality compared with the control group ($p = 0.005$). The DSWPD group also scored significantly higher on the BDI, indicating more depressive symptoms ($p = 0.007$) and scored lower on the Horne–Östberg Scale, consistent with a preference for eveningness ($p < 0.001$). Finally, there was no significant difference in subjective sleepiness as measured with the ESS between the two groups.

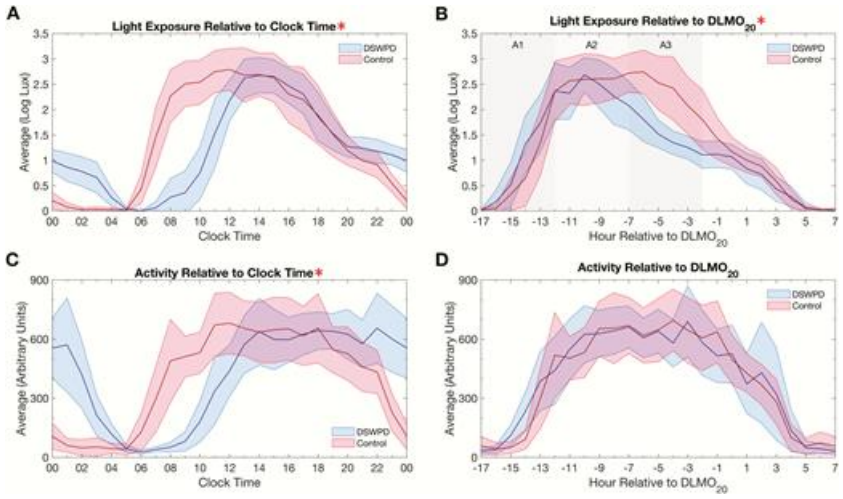
$DLMO_{20}$ was significantly later in the DSWPD group compared with controls ($p < 0.001$). $MLiT_{500}$ was significantly later in the DSWPD group

compared with controls ($p < 0.001$), but TAT_{1000} was not significantly different between groups. Neither of the phase angles (SS-$DLMO_{20}$, SE-$DLMO_{20}$) calculated were significantly different between groups.

24 hr light and activity comparisons

Using our GEE model, we found that individuals with DSWPD had later light exposure ($p < 0.001$) and activity ($p = 0.001$) patterns compared with controls relative to clock time (Figure 2, A and C). When light and activity were aligned by $DLMO_{20}$, light-exposure patterns (the timing of increase and decrease) on average occurred earlier across the entire 24 hr day for individuals with DSWPD compared with controls ($p = 0.03$), whereas activity patterns were not significantly different (Figure 2, B and D). This relationship of earlier light exposure in individuals with DSWPD compared with controls relative to $DLMO_{20}$ was driven by strong differences in the A3 subinterval (MT 17 to 22).

Figure 2.



View large Download slide

Light exposure and activity patterns relative to clock time and $DLMO_{20}$. Twenty-four hour light exposure and activity for the DSWPD and control groups averaged into 1 hr bins and presented in relation to clock time (A and C, respectively) and $DLMO_{20}$ (B and D, respectively). The lines represent the means for each group with the surrounding bands indicating the 95% confidence intervals. The red asterisks in the titles of the plots indicate where there is a significant difference in timing between groups ($p < 0.05$). The advance portion of the phase-response curve is broken down into three sequential nonoverlapping 5 hr subintervals noted as A1, A2, and A3 (respectively). $DLMO_{20}$ = dim light melatonin onset 20%.

Advancing and delaying light comparisons

Our statistical model showed significantly less light exposure across the entire advancing interval in individuals with DSWPD compared with controls ($p < 0.001$). When the three 5 hr advancing subintervals were assessed separately, individuals with DSWPD had no significant differences in light exposure for the first two subintervals (MT 7 to MT 17). In the third subinterval, individuals with DSWPD had significantly less light exposure compared with controls (MT 17 to MT 22; $p = 0.001$). There was a trend of decreased light exposure during the delay interval in individuals with DSWPD compared with controls ($p = 0.08$).

As shown in Table 2, there was no significant difference in the percentage of days with at least one advancing light pulse or the average pulse intensity between the DSWPD and control groups. Individuals with DSWPD had a later average pulse start time relative to clock time ($p < 0.001$) and an earlier pulse start time relative to $DLMO_{20}$ ($p = 0.001$) compared with controls. Across the entire advancing interval, individuals with DSWPD had fewer light pulses ($p = 0.02$) and a trend towards shorter total pulse time ($p = 0.08$) compared with controls. However, pulse length was not significantly different. The trend towards shorter total pulse time across the entire advancing interval in individuals with DSWPD compared with controls at 200 lux was also present at thresholds from 20 to 220 lux ($p = 0.053$–0.094).

Table 2.

Advancing and delaying light pulse characteristics for DSWPD/control groups

	DSWPD (*n* = 12)	Control (*n* = 12)	*P*
Days w/ Pulses (%)	93% (15%)	97% (8%)	0.4
Pulse Start by Clock Time (hh:mm)	15:12 (0:51)	12:38 (0:39)	<0.001
Pulse Start by Melatonin Time (hr)	14.9 (1.32)	16.58 (0.85)	0.001
Advance Interval (MT 7 to 22)			
# of Pulses	5.57 (2.79)	10.89 (4.77)	0.024
Pulse Length (min)	16.91 (10.18)	17.89 (16.44)	0.86
Total Pulse Time (min)	95.30 (61.26)	172.75 (73.37)	0.083
Pulse Intensity (lux)	1517.47 (1135.65)	1473.55 (1219.14)	0.92
A1 Subinterval (MT 7 to 12)			
# of Pulses	0.73 (NR)	0.79 (NR)	0.89
Pulse Length (min)	21.08 (NR)	16.01 (NR)	0.54
Total Pulse Time (min)	11.47 (NR)	12.67 (NR)	0.86
Pulse Intensity (lux)	1997.46 (NR)	1159.50 (NR)	0.35
A2 Subinterval (MT 12 to 17)			
# of Pulses	3.38 (2.04)	5.12 (2.79)	0.074
Pulse Length (min)	20.14 (6.52)	22.52 (17.66)	0.78
Total Pulse Time (min)	69.11 (44.33)	102.70 (50.90)	0.27
Pulse Intensity (lux)	1832.52 (411.94)	1784.63 (846.11)	0.94
A3 Subinterval (MT 17 to 22)			
# of Pulses	1.46 (1.31)	4.97 (3.39)	0.003
Pulse Length (min)	10.26 (11.57)	12.63 (15.39)	0.46
Total Pulse Time (min)	14.72 (33.25)	57.38 (54.17)	0.002
Pulse Intensity (lux)	782.40 (996.59)	1203.85 (640.27)	0.24
Delay Interval (MT 22 to 7)			
# of Pulses	0.33 (NR)	1.65 (NR)	0.022
Pulse Length (min)	4.84 (NR)	11.19 (NR)	0.038
Total Pulse Time (min)	2.01 (NR)	17.4 (NR)	0.006
Pulse Intensity (lux)	287.68 (NR)	595.06 (NR)	0.088

Standard deviations are represented in parentheses. The advance portion of the phase-response curve is broken down into three sequential nonoverlapping 5 hr subintervals noted as A1, A2, and A3 (respectively). Day-to-day variability was not reported for light pulse variables in A1 or the delay interval due to the low number of light pulses at these times.

DSWPD = delayed sleep-wake phase disorder; MT = melatonin time (relative to $DLMO_{20}$); NR = not reported.

View Large

With the advance interval split into three smaller 5 hr subintervals, there was no difference in advancing light pulse characteristics (number, length, and total time) between the DSWPD and control groups for the first two subintervals (MT 7 to MT 17). In the third subinterval (MT 17 to MT 22), individuals with DSWPD had significantly fewer light pulses ($p = 0.003$) and a shorter total pulse time ($p = 0.003$) compared with controls, but pulse length was not significantly different. The relationship of shorter total pulse time during the A3 subinterval in individuals with DSWPD compared with controls at 200 lux was also present at thresholds from 60 to 1000 lux ($p = 0.002$–0.038).

In the delay interval, individuals with DSWPD had fewer light pulses ($p = 0.02$) of a shorter length ($p = 0.04$) resulting in a reduced total pulse time ($p = 0.006$) compared with controls. There was a trend of lower pulse intensity in the delay interval in individuals with DSWPD compared with controls ($p = 0.09$). The relationship of shorter total pulse time during the delay interval in individuals with DSWPD compared with controls at 200 lux was also present from 160 to 1000 lux ($p = 0.002$–0.032).

The day-to-day variability of the number of light pulses was higher in controls compared with individuals with DSWPD across the entire advancing interval ($p = 0.015$) as well as during the A3 subinterval ($p < 0.001$). Day-to-day variability was not significantly different for other light pulse variables (pulse length, total pulse time, or pulse intensity) or at other times (A1, A2, or the delay interval). Day-to-day variability was not reported for light pulse variables in A1 or the delay interval due to the low number of light pulses at these times.

$DLMO_{20}$ to sleep midpoint interval

The mean interval between $DLMO_{20}$ and sleep midpoint was 7 hr 23 min (±1 hr 13 min) and there was no significant difference in the distribution of this interval between individuals with DSWPD and controls. The Weibull model fit to $N = 24$ observations of the interval between $DLMO_{20}$ and sleep midpoint was estimated to have scale and shape parameters $k = 6.43$ and $\lambda = 7.91$, respectively. Both goodness-of-fit tests passed with $p < 0.05$ and were confirmed by diagnostic plots. From these parameters, we estimate that 98.9 per cent of individuals will have an interval between $DLMO_{20}$ and sleep midpoint of less than or equal to 10 hr.

Discussion

To the best of our knowledge, this is the first study to examine the relationship between habitual light exposure and endogenous circadian phase in individuals with DSWPD and controls. As expected, light exposure and activity patterns were later in individuals with DSWPD compared with controls relative to clock time. Contrary to our hypothesis, individuals with DSWPD had an earlier light-exposure pattern compared with controls relative to melatonin timing (MT; defined as $DLMO_{20}$), but this relationship was predominantly driven by decreased exposure from MT 17 to 22. Using a previously published human PRC to light as a reference [25], individuals with DSWPD were exposed to less light in the advancing portion of the PRC compared with controls. The largest differences were seen in the late advancing window, which corresponds with a later average clock time in individuals with DSWPD (17:18 to 22:18) compared with controls (13:03 to 18:03). Differences in advancing light signaling within this window were due to fewer light pulses and less total pulse time in individuals with DSWPD compared with controls. There was a trend for decreased light exposure in the delaying portion of the PRC in individuals with DSWPD compared with controls, which was due to fewer light pulses, a shorter average pulse length, and less total pulse time during this interval.

In our study, the pattern of light exposure relative to clock time showed higher levels of light in the evening and lower levels in the morning, which is similar to the 24 hr patterns reported in prior studies in adults and adolescents with DSWPD [20, 29]. In the study by Auger and colleagues, individuals with DSWPD were exposed to more light at night (22:00 to 2:00) and less light in the morning (8:00 to 9:00 and 10:00 to 12:00). Similarly, the study by Joo and colleagues found increased light exposure at night (2:00 to 4:00) and decreased light exposure in the morning (8:00 to 11:00).

To interpret the possible impact of decreased advancing light exposure on circadian timing in individuals with DSWPD, it is helpful to review the mechanism of circadian rhythm entrainment. Most young and middle-aged adults have a circadian period that is longer than 24 hr [2, 4], and so daily phase advances are necessary to maintain stable entrainment to the 24 hr light/dark cycle. Recent evidence further supports the notion that individuals with DSWPD have a longer circadian period length on average than intermediate types [30], which would necessitate more robust daily phase–advancing signals, such as light, to maintain stable 24 hr entrainment. Our data demonstrate that individuals with DSWPD were actually exposed to less light in the late advance region compared with intermediate controls, which could result in a delayed sleep-wake rhythm relative to the environment and social-activity schedules. Given this increased tendency to phase delay, it is possible that individuals with DSWPD find it more difficult to maintain stable entrainment compared with controls. Most sighted individuals with non-24 hr sleep-wake disorder are initially diagnosed with DSWPD or present with delayed sleep-wake patterns, and a number have recurrent intermittent periods in which their sleep-wake time appears

to be stably delayed for several weeks [31]. This phenotypic overlap between the two disorders may be reflective of less robust entrainment in individuals with DSWPD. In addition, other factors such as changes in the sensitivity of the circadian system to light, differences in the homeostatic regulation of sleep, and behavioral or environmental influences likely affect entrainment in these patients [32].

The time interval in which the advancing stimulus is diminished, i.e. the last third of the advancing interval of the PRC, may be of particular clinical importance. Current treatment options for DSWPD include bright light therapy, which aims to advance circadian timing by targeting the advancing portion of the PRC. However, due to the lack of practical ways to assess endogenous circadian timing, clinicians will often instruct their patients to administer light exposure on habitual awakening for 1–2 hr. This approach has shown mixed efficacy in several studies, and relapse is common [33–36]. Our data suggest that rather than exclusively targeting the early advancing window (in which individuals with DSWPD are exposed to equivalent intensities of light to controls on a habitual basis) for intervention, patients may also benefit from increased bright light exposure later in the advancing window. To estimate the appropriate timing for bright light exposure, one can use sleep midpoint (derived from sleep logs and/or actigraphy). Using our data on the interval between $DLMO_{20}$ and sleep midpoint, we propose that the light exposure prior to sleep midpoint + 12 hr will fall within the advancing window in 98.9 per cent of individuals. This could be evaluated in future studies as a potential method for estimating circadian phase and improving the effectiveness of light therapy in the clinic.

Exposure to light is not only influenced by sleep and wake timing, but also by work and school schedules. Although direct data on specific behaviors were not collected in this study, it is likely that in the A1 subinterval (MT 7 to 12) participants were sleeping, and in the A2 subinterval (MT 12 to 17) individuals were following work/school schedules. The emergence of significant differences in light exposure in the A3 subinterval (MT 17 to 22) is likely influenced by a decline in natural light in the latter half of the day, which occurs at an earlier time relative to $DLMO_{20}$ in individuals with DSWPD.

The data in this study were collected from 2004 to 2007, which was before the prevalent use of personal light–emitting devices [37]. A recent study showed that usage of light emitting devices in the 3 hr prior to bedtime and exposure to light after DLMO was higher in young adults with delayed sleep time compared with controls [38]. In the present environment, light exposure from tablets, laptops, and cell phones in the evening and night undoubtedly contributes to delayed sleep phase [39, 40]. The finding in our study that individuals with DSWPD had decreased light exposure during the late advancing window (A3) indicates that in addition to the current clinical recommendation to avoid exposure to light prior to bedtime, increasing light in the late advancing window may help enhance compliance and long-term effectiveness of light therapy in DSWPD.

We based our estimation of advancing and delaying light exposure on the PRC constructed by St. Hilaire and colleagues which used light pulses lasting 1 hr at 8000 lux [25]. That stimulus is brighter with a longer duration than the average pulses found in this study, which could affect the accuracy of our prediction of the phase advancing and delaying windows. If we used the PRC constructed by Khalsa and colleagues with a 6.7 hr bright light stimulus as previously referenced in the literature on habitual light exposure in morning and evening types [5, 23], we would have concluded that individuals with DSWPD were exposed to less delaying light relative to controls. We chose to refer to the St. Hilaire PRC because the duration of the light stimulus used was most similar to the pulse length observed in our field study among the available PRCs in adults. Crowley and Eastman recently published a PRC in adolescents using four 20 min bright light stimuli separated by 10 min intervals of dim light [41]. The timing of the advance and delay windows in this PRC is very similar to the St. Hilaire PRC, and applying the PRC to our results would similarly indicate that the key differences we found during the A3 subinterval fall within the late advance region. An additional consideration is that these PRCs were constructed in healthy participants, as there are no published PRCs to light in individuals with DSWPD. Regardless of which PRC is used to analyze these results, our data indicate that contrary to the common clinical assumption that individuals with DSWPD receive greater light exposure during the biological evening [33], they may actually be exposed to less light at this time. This suggests that factors other than environmental light exposure are likely playing a role in the pathophysiology of DSWPD, including altered sensitivity to light [34, 42]. Additionally, differences between the St. Hilaire and Khalsa PRCs suggest that it may be more effective to target the late advancing window with short light pulses. Previous research suggests that short intermittent light exposures can be just as effective and more time efficient at resetting the circadian clock compared with longer continuous exposures [43].

Limitations of our study include the fact that the actigraphy-derived measurements in this study reflect environmental light exposure at the wrist, which may differ from retinal light exposure. In addition, we excluded individuals with Axis-I DSM diagnoses, which may limit the generalizability of the results to DSWPD patients with comorbid psychiatric disorders [44]. Finally, the sample size of this study together with the high variability of certain measurements may have limited the power to detect differences in other outcomes.

Our results indicate that light-exposure patterns, particularly decreased exposure to late advancing light pulses, may play an important role in the development and perpetuation of the delayed sleep-wake timing relative to 24 hr social and environmental cycles in patients with DSWPD. Thus, a strategy that targets light exposure in the late advance region using short intermittent pulses has the potential to be a practical and effective addition to current treatment recommendations for DSWPD.

Funding

This study was supported the National Institute of Health's National Center for Advancing Translational Sciences (UL1TR000150) and National Heart, Lung, and Blood Institute (HL069988). Additional support was provided by the Northwestern University Feinberg School of Medicine Center for Circadian and Sleep Medicine.

Acknowledgments

The authors would like to acknowledge the nurses and staff of the Clinical Research Unit at Northwestern Memorial Hospital for their hard work performing their duties for this study.

Conflict of interest statement. None declared.

References

1. Lowrey PL, et al. Mammalian circadian biology: elucidating genome-wide levels of temporal organization. *Annu Rev Genomics Hum Genet* . 2004;5:407–441.
   Google Scholar Crossref PubMed

2. Duffy JF, et al. Entrainment of the human circadian system by light. *J Biol Rhythms* . 2005;20(4):326–338.
   Google Scholar Crossref PubMed

3. Pittendrigh CS, et al. A functional analysis of circadian pacemakers in nocturnal rodents. *J Comp Physiol A* . 1976;106(3):333–355.
   Google Scholar Crossref

4. Roenneberg T, et al. The art of entrainment. *J Biol Rhythms* . 2003;18(3):183–194.
   Google Scholar Crossref PubMed

5. Khalsa SB, et al. A phase response curve to single bright light pulses in human subjects. *J Physiol* . 2003;549(Pt 3):945–952.
   Google Scholar Crossref PubMed

6. Honma K, et al. A human phase response curve for bright light pulses. *Jpn J Psychiatry Neurol* . 1988;42:167–168.

7. Benloucif S, et al. Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. *J Biol Rhythms* . 2005;20(2):178–188.
   Google Scholar Crossref PubMed

8. American Academy of Sleep Medicine. *International Classification of Sleep Disorders: Diagnostic and Coding Manual* . 3rd ed. Vol. 281. 2014. doi:https://doi.org/10.1111/febs.12678

9. Paine SJ, et al. Identifying advanced and delayed sleep phase disorders in the general population: a national survey of New Zealand adults. *Chronobiol Int* . 2014;31(5):627–636.
   Google Scholar Crossref PubMed

10. Danielsson K, et al. Delayed sleep phase disorder in a Swedish cohort of adolescents and young adults: prevalence and associated factors. *Chronobiol Int* . 2016;33(10):1331–1339.

Google Scholar Crossref PubMed

11. American Psychiatric Association. *DSM-V* . 2013. doi:https://doi.org/10.1176/appi.books.9780890425596.744053

12. van Maanen A, et al. Chronic sleep reduction in adolescents with delayed sleep phase disorder and effects of melatonin treatment. *Sleep Biol Rhythms* . 2013;11(2):99–104.
Google Scholar Crossref

13. Weitzman ED, et al. Delayed sleep phase syndrome. A chronobiological disorder with sleep-onset insomnia. *Arch Gen Psychiatry* . 1981;38(7):737–746.
Google Scholar Crossref PubMed

14. Wyatt JK, et al. Circadian phase in delayed sleep phase syndrome: predictors and temporal stability across multiple assessments. *Sleep* . 2006;29(8):1075–1080.
Google Scholar Crossref PubMed

15. Ozaki S, et al. Prolonged interval from body temperature nadir to sleep offset in patients with delayed sleep phase syndrome. *Sleep* . 1996;19(1):36–40.
Google Scholar PubMed

16. Uchiyama M, et al. Altered phase relation between sleep timing and core body temperature rhythm in delayed sleep phase syndrome and non-24-hour sleep-wake syndrome in humans. *Neurosci Lett* . 2000;294(2):101–104.
Google Scholar Crossref PubMed

17. Watanabe T, et al. Sleep and circadian rhythm disturbances in patients with delayed sleep phase syndrome. *Sleep* . 2003;26(6):657–661.
Google Scholar Crossref PubMed

18. Oren DA, et al. Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome. *J Neurol Neurosurg Psychiatry* . 1995;58(3):379.
Google Scholar Crossref PubMed

19. Shibui K, et al. Melatonin rhythms in delayed sleep phase syndrome. *J Biol Rhythms* . 1999;14(1):72–76.
Google Scholar Crossref PubMed

20. Auger RR, et al. Light exposure among adolescents with delayed sleep phase disorder: a prospective cohort study. *Chronobiol Int* . 2011;28(10):911–920.
Google Scholar Crossref PubMed

21. Joo EY, et al. Timing of light exposure and activity in adults with delayed sleep-wake phase disorder. *Sleep Med* . 2017;32:259–265.
Google Scholar Crossref PubMed

22. American Association of Sleep Medicine (AASM). *The International Classification of Sleep Disorders: Diagnostic and Coding Manual, ICSD-2* . 2005.

23. Goulet G, et al. Daily light exposure in morning-type and evening-type individuals. *J Biol Rhythms* . 2007;22(2):151–158.
Google Scholar Crossref PubMed

24. Reid KJ, et al. Timing and intensity of light correlate with body weight in adults. *PLoS One* . 2014;9(4):1–11.

25. St Hilaire MA, et al. Human phase response curve to a 1 h pulse of bright white light. *J Physiol* . 2012;590(13): 3035–3045.
Google Scholar Crossref PubMed

26. Diggle PJ, et al. *Analysis of Longitudinal Data* . New York: Oxford University Press; 1994.

27. Delignette-Muller ML, et al. fitdistrplus: an R package for fitting distributions. *J Stat Softw* . 2015;64(4):1–34.

28. Stephens MA. Tests based on edf statistics. In: D'Agostino R, StephensM, eds. *Goodness-of-Fit Techniques* . Vol. 68. New York: Marcel Dekker; 1986:97–185.

29. Joo EY, et al. Timing of light exposure and activity in adults with delayed sleep-wake phase disorder. *Sleep Med* . 2017;32:259–265.
Google Scholar Crossref PubMed

30. Micic G, et al. Circadian melatonin and temperature taus in delayed sleep-wake phase disorder and non-24-hour sleep-wake rhythm disorder patients: an ultradian constant routine study. *J Biol Rhythms* . 2016;31(4):387–405.
Google Scholar Crossref PubMed

31. Malkani RG, et al. Diagnostic and treatment challenges of sighted non-24-hour sleep-wake disorder. *J Clin Sleep Med* . 2018;14(4):603–613.
Google Scholar Crossref PubMed

32. Micic G, et al. The etiology of delayed sleep phase disorder. *Sleep Med Rev* . 2016;27:29–38.
Google Scholar Crossref PubMed

33. Sack RL, et al. ; American Academy of Sleep Medicine. Circadian rhythm sleep disorders: part II, advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder, and irregular sleep-wake rhythm. An American Academy of Sleep Medicine review. *Sleep* . 2007;30(11):1484–1501.
Google Scholar Crossref PubMed

34. Dagan Y, et al. Circadian rhythm sleep disorders: toward a more precise definition and diagnosis. *Chronobiol Int* . 1999;16(2):213–222.
Google Scholar Crossref PubMed

35. Lack L, et al. Morning blue light can advance the melatonin rhythm in mild delayed sleep phase syndrome. *Sleep Biol Rhythms* . 2007;5(1):78–80.
Google Scholar Crossref

36. Sharkey KM, et al. Effects of an advanced sleep schedule and morning short wavelength light exposure on circadian phase in young adults with late sleep schedules. *Sleep Med* . 2011;12(7):685–692.
Google Scholar Crossref PubMed

37. Tosini G, et al. Effects of blue light on the circadian system and eye physiology. *Mol Vis* . 2016;22:61–72.
Google Scholar PubMed

38. Van der Maren S, et al. Daily profiles of light exposure and evening use of light-emitting devices in young adults complaining of a delayed sleep schedule. *J Biol Rhythms* . 2018;33(2):192–202.
Google Scholar Crossref PubMed

39. Wright KPJ, et al. Entrainment of the human circadian clock to the natural light-dark cycle. *Curr Biol* . 2013;23(16):1554–1558.
Google Scholar Crossref PubMed

40. Stothard ER, et al. Circadian entrainment to the natural light-dark cycle across seasons and the weekend. *Curr Biol* . 2017;27(4):508–513.
Google Scholar Crossref PubMed

41. Crowley SJ, et al. Human adolescent phase response curves to bright white light. *J Biol Rhythms* . 2017;32(4):334–344.
Google Scholar Crossref PubMed

42. Aoki H, et al. Hypersensitivity of melatonin suppression in response to light in patients with delayed sleep phase syndrome. *Chronobiol Int* . 2001;18(2):263–271.
Google Scholar Crossref PubMed

43. Chang AM, et al. Human responses to bright light of different durations. *J Physiol* . 2012;590(13):3103–3112.
Google Scholar Crossref PubMed

44. Reid KJ, et al. Systematic evaluation of Axis-I DSM diagnoses in delayed sleep phase disorder and evening-type circadian preference. *Sleep Med* . 2012;13(9):1171–1177.
Google Scholar Crossref PubMed

Topic:

melatonin

pulse

sleep

light exposure

actigraphy

Issue Section: Circadian Rhythms and Circadian Disorders

View Metrics

Subject alert

Receive exclusive offers and updates from Oxford Academic

More on this topic

Two- and 4-Hour Bright-Light Exposures Differentially Effect Sleepiness and Performance the Subsequent Night

Circadian Rhythms of Melatonin, Cortisol, and Clock Gene Expression During Simulated Night Shift Work

Non-24-Hour Sleep-Wake Syndrome in a Sighted Man: Circadian Rhythm Studies and Efficacy of Melatonin Treatment

Actigraphic detection of periodic limb movements: development and validation of a potential device-independent algorithm. A proof of concept study

Related articles in

Google Scholar

Related articles in PubMed

All that wheezes at night is not asthma.

Sleep macro-architecture and micro-architecture in children born preterm with sleep disordered breathing.

Sleep Deprivation caused a Memory Defects and Emotional Changes in a Rotenone-based Zebrafish Model of Parkinson's Disease.

Citing articles via

Google Scholar

CrossRef

Latest | **Most Read** | **Most Cited**

Characterization of the sleep disorder of anti-IgLON5 disease

Actigraphic detection of periodic limb movements: development and validation of a potential device-independent algorithm. A proof of concept study

Simultaneous tonic and phasic REM sleep without atonia best predicts early phenoconversion to neurodegenerative disease in idiopathic REM sleep behavior disorder

Residual symptoms after natural remission of insomnia: associations with relapse over 4 years

Sleep duration and fragmentation in relation to leukocyte DNA methylation in adolescents

Online ISSN 1550-9109
Print ISSN 0161-8105