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Original Article

Sleep and circadian variability in people with delayed sleep–wake phase disorder versus healthy controls

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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 ten-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 ($p \leq 0.015$). Intraindividual variability in sleep onset time and sleep efficiency was similar between the two groups ($p \geq 0.30$). 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.
Clinical trial: Circadian Phase Assessments at Home, http://clinicaltrials.gov/show/NCT01487252, NCT01487252.

1. 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 h 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

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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 (Fig. 2 in Ref. [23]).

We recently completed a ten 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. 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 ≤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 traveled 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 ten-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 (±30 min), 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.

Table 1
Baseline characteristics of the healthy control and delayed sleep–wake phase disorder participants.

	Controls	Delayed sleep–wake phase disorder	Group difference
	Mean (S.D.)	Mean (S.D.)	
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^2)	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)	**$p < 0.001$**
Average prestudy sleep onset (h:mm)	23:40 (0.94)	02:44 (2.4)	**$p < 0.001$**
Average prestudy wake time (h:mm)	07:47 (0.6)	09:49 (1.4)	**$p < 0.001$**
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)	**$p < 0.001$**

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.