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Original Article

Sleep regularity is associated with sleep-wake and circadian timing, and mediates daytime function in Delayed Sleep-Wake Phase Disorder

Jade M. Murray [a, b, c], Andrew J.K. Phillips [a, *], Michelle Magee [a, b, c], Tracey L. Sletten [a, b, c], Christopher Gordon [b, c, d, e], Nicole Lovato [b, f], Bei Bei [a], Delwyn J. Bartlett [b, c, d], David J. Kennaway [g], Leon C. Lack [b, f], Ronald R. Grunstein [b, c, d], Steven W. Lockley [a, b, c, h, i], Shantha M.W. Rajaratnam [a, b, c, h, i] for the Delayed Sleep on Melatonin (DelSoM) Study Group[1]

[a] School of Psychological Sciences, Monash University, Clayton, Victoria, Australia
[b] Cooperative Research Centre for Alertness, Safety and Productivity, Clayton, Victoria, Australia
[c] NHMRC Centre for Sleep and Circadian Neurobiology, Sydney, New South Wales, Australia
[d] Woolcock Institute of Medical Research and Sydney Local Health District, Sydney, New South Wales, Australia
[e] University of Sydney Susan Wakil School of Nursing, New South Wales, Australia
[f] Adelaide Institute for Sleep Health, College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia
[g] Robinson Research Institute and School of Medicine, University of Adelaide, Adelaide, South Australia, Australia
[h] Division of Sleep and Circadian Disorders, Departments of Medicine and Neurology, Brigham and Women's Hospital, Boston, MA, USA
[i] Division of Sleep Medicine, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Background: In healthy populations, irregular sleep patterns are associated with delayed sleep and poor functional/mood outcomes. Currently, it is unknown whether irregular sleep contributes to poor functional/mood outcomes in individuals with Delayed Sleep-Wake Phase Disorder (DSWPD).
Methods: In 170 patients with DSWPD, we collected sleep-wake patterns, dim light melatonin onset (DLMO), and functional/mood outcomes. The Sleep Regularity Index (SRI) and other sleep timing metrics were computed. Correlations of SRI were computed with phase angle (difference between DLMO and desired bedtime), sleep timing and quality variables, daytime function, sleep-related daytime impairment, mood, and insomnia symptom severity. Path analyses assessed whether SRI or total sleep time mediated the associations between sleep onset time and phase angle with daytime functioning, sleep-related impairment, and mood outcomes.
Results: Higher SRI was associated with earlier sleep and longer total sleep time, but did not relate to sleep quality, daytime function, or mood outcomes. Path analysis showed that phase angle was directly associated with all outcome variables, whereas sleep onset time was not directly associated with any. SRI mediated the effects of sleep onset time and phase angle on daytime function. Total sleep time mediated the effects of sleep onset time and phase angle on sleep-related impairment.
Conclusion: Individuals with DSWPD who have more delayed sleep and a greater phase angle also have more irregular sleep. This suggests that it is not delayed sleep timing *per se* that drives poor functional outcomes in DSWPD, but rather the timing of sleep relative to circadian phase and resultant irregular sleep patterns.

1. Introduction

There is substantial inter-individual variability in sleep and circadian timing in the human population, as well as the phase angle between sleep and circadian timing [1–4]. Accumulating evidence shows that there is also considerable intra-individual

* Corresponding author. Monash Institute of Cognitive and Clinical Neurosciences, School of Psychological Sciences, 18 Innovation Walk, Monash University, Clayton, Victoria, 3800, Australia.
E-mail address: andrew.phillips@monash.edu (A.J.K. Phillips).
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variability in sleep timing, which may exceed inter-individual variability [5–7]. Intra-individual variability often arises due to large discrepancies between sleep timing on work vs. free days, termed 'social jetlag' [8]. This occurs when individuals sleep later and/or longer on free days, when unrestricted by work or other obligations, in an attempt to catch up on lost sleep [9–11]. Increasingly, however, research is indicating that irregular sleep patterns are as detrimental as insufficient sleep [12].

A recent systematic review reported that large daily variability in measures such as bed and wake time, sleep duration, and sleep onset latency are associated with detrimental physical and mental health outcomes [13]. For example, greater night-to-night variability in sleep timing and duration is linked to increased risk of heart disease, diabetes, and obesity [14–16], as well as blunted diurnal cortisol rhythms [17]. Intra-individual variability in sleep duration and timing has also been linked to worse cognitive function and academic performance [18–23], and increased incidence and severity of affective disorders such as depression [5,24–26]. Mental illness [18], and stress [27] are also associated with greater intra-individual variability in sleep timing and duration, and in adolescents it is strongly associated with poorer psychological wellbeing [28,29]. Similarly, challenging behavior observed in children with low-functioning autism is strongly positively associated with daily sleep timing variability [30].

A novel measure of variability in sleep timing, the Sleep Regularity Index (SRI), was developed to capture variation on a circadian timescale [22]. The SRI compares sleep patterns in each 24 h period with each subsequent 24 h period to determine their similarity. In college students, higher SRI (ie, more regular sleep) was found to associate with earlier sleep timing, earlier circadian phase, higher amplitude daily light/dark patterns, better academic performance [22], and improved daily mood ratings [31].

DSWPD is characterized by a marked delay in sleep and wake times that are sometimes also associated with a delay in the endogenous circadian pacemaker [32]. We and others [33,34] have shown that almost half of patients diagnosed using standard diagnostic criteria did not have a delay in dim light melatonin onset (DLMO) relative to desired bedtime, and identified two phenotypes of the disorder. On this basis, we previously defined a 'circadian group' for DSWPD (those with a circadian phase delay relative to their desired bedtime) and a 'non-circadian group' (those without a circadian phase delay relative to their desired bedtime) [35]. In the circadian group, we found later sleep-wake and circadian timing, increased severity of disorder, and greater depressive symptom severity [35].

Sleep regularity is currently given little consideration in the screening, diagnosis, or treatment of DSWPD, despite a number of the key symptoms and characteristics of DSWPD being associated with irregular sleep in other populations. Large discrepancies in observed bed and wake times between work and free days in DSWPD [32] are indicative of high day-to-day variability, which could contribute to poor outcomes. Assessment and improvement of sleep regularity may therefore facilitate improved clinical diagnosis and treatment targets for DSWPD.

The current study aimed to determine the relationships between sleep regularity and sleep and circadian timing in individuals with DSWPD, as well as functional, sleep-related impairment, and mood outcomes. Additionally, we sought to investigate the potential underlying mechanisms of these relationships using path analysis.

2. Materials and methods

This multi-center study, approved by the Monash University Human Research Ethics Committee, The University of Sydney Human Research Ethics Committee, Southern Adelaide Clinical Human Research Ethics Committee, and The University of Adelaide Human Research Ethics Committee, was part of a larger randomized controlled trial testing the efficacy of exogenous melatonin for DSWPD, Delayed Sleep on Melatonin (DelSoM) Study Group (ACTRN12612000425897). Participants provided written informed consent and were reimbursed for study-related expenses. These data have been described previously [35,36].

2.1. Participants

Participants were recruited from a community sample by responding to study advertisements at three study sites: Melbourne (Monash University), Sydney (Woolcock Institute of Medical Research), and Adelaide (Flinders University). The study was advertised via radio, newspaper, television, and posters. Sleep physicians, general practitioners, and psychologists were also invited to refer patients meeting preliminary criteria for the study. In total, 185 participants aged 16–64 years, with a body mass index (BMI) between 18 and 35 kg/m^2, and who met diagnostic criteria for DSWPD [37], were recruited. Additionally, participants were included only if they were employed (including paid, unpaid, volunteer work, homemaker, or training) or undertaking study (school or university) a minimum of five days a week. Participants who did not work or study regular hours (defined as all work hours falling between 6 am and 11 pm) were excluded. Detailed inclusion and exclusion criteria have been reported previously [35,36].

2.2. Screening

Respondents to study advertising completed an online preliminary screening questionnaire to assess risk of DSWPD. Those who were deemed at risk for DSWPD were then telephone screened and if the eligibility criteria were met, invited to participate in the study. Participants attended a formal consent and screening interview, in which they were diagnosed according to the International Classification of Sleep Disorders-2 [ICSD-2; [37]] via clinical interview with a sleep physician. Participants completed questionnaires to assess mood, daytime function, habitual sleep-wake habits, lifestyle habits, past and current physical and mental health status.

2.3. Sleep-wake assessment

At home sleep-wake assessment was completed by participants for a minimum of seven days prior to a laboratory visit using wrist actigraphy (Actiwatch Spectrum, Philips Respironics, Bend, OR, USA) and sleep diaries. During this period, participants maintained their habitual sleep-wake schedule. Bed and wake times in actigraphy were identified using the times reported in sleep diaries, from which the following variables were generated: bedtime, sleep onset time, midsleep, wake time, total sleep time, sleep onset latency, sleep efficiency, and wake after sleep onset. In the case of discrepancies between sleep diaries and actigraphy, the following process was applied: if subjective bedtime was reported as $\geq$60 min before a substantial reduction in activity and light levels, bedtime was adjusted to the time of the decrease in activity and light. If reported wake time was $\geq$60 min after a substantial increase in activity and light, wake time was shifted to the start of the sustained activity and light increase. These timings were determined via visual inspection by an independent researcher and then resolved by two study researchers (JM and MM) [35,36].

2.4. Circadian phase assessment

Circadian phase was assessed via salivary dim light melatonin onset (DLMO). Participants attended an ~8-h laboratory visit immediately following the seven days of at-home sleep-wake monitoring. Participants arrived 5.5 h prior to habitual bedtime and were discharged 2.5 h after habitual bedtime. During this time, participants remained in dim light (<3 lux) and instructed to remain in an upright seated position to control posture. Participants were permitted to move for 10 min after each saliva sample to allow for bathroom breaks. Saliva samples (Salivette, Sarstedt, Numbrecht, Germany) were taken every hour, from 5 h prior to habitual bedtime until 2 h after. Samples were centrifuged and stored at −20 °C immediately after collection and assayed using the radioimmunoassay method [38] within one week of collection. DLMO was calculated as the time that melatonin concentrations crossed and remained above a threshold of 2.3 pg/mL, calculated from linear interpolation between the samples immediately before and after the threshold [39]. Details of the method for calculating DLMO, as well as the limit of detection of the assay and the inter-assay CVs have previously been reported [35,36].

Based on the phase angle difference (time elapsed between two measured variables) between DLMO time and desired or required bedtime, participants were classified into two groups, following a previous classification method [35]. Desired bedtime was self-reported by participants and defined as the time a participant felt they would need to go to bed on a night before school or work in order to feel fully rested the next day. The “circadian” group included participants for whom DLMO occurred 30 min before, or any time after, desired bedtime. The “non-circadian” group included participants for whom DLMO occurred more than 30 min before desired bedtime.

2.5. Sleep Regularity Index (SRI)

Sleep regularity was quantified using the Sleep Regularity Index (SRI) [22], which compares time-points 24 h apart and computes the likelihood that they are in the same state (sleep vs. wake). Index scores are scaled to give a percentage probability of an individual being in the same state, such that the maximum score is 100 (perfect regularity), and the minimum is 0 (completely random). Sleep and wake states were determined using actigraphy data with 1-min epochs, using the Actiware 5 software algorithm (Philips Respironics, Bend, OR). The actigraphy data had been adjusted according to sleep and wake times reported in sleep diaries, as described above. Since some participants had missing data (eg, due to removal of the actiwatch), participants were required to have a minimum of 96 h of cumulative time-point comparisons, otherwise the SRI value was treated as missing.

2.6. Mood

Depression was assessed with the Beck Depression Inventory, Second Edition (BDI-II; [40]), a 21 item self-report measure assessing the severity of depressive symptoms experienced in the last two weeks. Anxiety was assessed using the Beck Anxiety Inventory (BAI; [41]), which is also comprised of 21 items that relate to anxiety, and are rated and scored in the same way as the BDI-II.

2.7. Daytime function, sleep-related impairment, and symptom severity

The Sheehan Disability Scale [42] was used to measure daytime functional outcomes. Participants indicate the extent to which the symptoms of the disorder are impairing their ability to function across three domains: work/school, social life, and family responsibilities. Additionally, the scale includes a measure of Absenteeism (number of days absent from work/school in the past month) and a measure of Presenteeism (number of days they were unproductive at work/school in the past month).

Sleep-related impairment was assessed using the Epworth Sleepiness Scale (ESS; [43]) and the Patient Reported Outcomes Measurement Information System (PROMIS; [44]). The ESS is a measure of daytime sleepiness in which patients rate the likelihood of falling asleep in eight different situations. The PROMIS is a multidimensional measurement tool that assesses several different domains, including Physical, Mental and Social health and under each domain are a number of sub-domains. The Physical Health sub-domain of sleep-related daytime impairments was used to measure sleepiness, irritability and difficulty concentrating.

Symptom severity was assessed using the Insomnia Severity Index (ISI; [45]).

The ESS, Sheehan Disability Scale and ISI were completed at consent, prior to the seven day at-home sleep-wake assessment. The BDI-II, BAI and PROMIS were completed on the last day of the at-home sleep-wake assessment, prior to attending the laboratory for circadian phase assessment.

2.8. Path analysis

To gain additional insights, we investigated plausible relationships between the sleep and circadian variables and mood and daytime function outcome measures, with three key outcome variables: (i) Absenteeism; (ii) ESS; and (iii) BDI-II.

We performed a path analysis involving four sleep/circadian variables: (i) the desired bed time (DBT)-DLMO phase angle difference; (ii) sleep onset time; (iii) SRI, and, (iv) total sleep time. We assumed that phase angle would drive differences in sleep onset time, since a later wake maintenance zone would contribute to later sleep onset [46–49]. Furthermore, we assumed that total sleep time depends on a combination of the other three variables, since biological time (phase angle), clock time (sleep onset time), and variability in sleep timing (SRI) could all influence sleep initiation, nighttime maintenance of sleep, and morning interruption by other events. Standardized β coefficients are reported for all paths, as well as p-values obtained from boot-strapping (1000 iterations).

We hypothesized that a later DLMO relative to DBT (ie, decreased phase angle), delayed sleep, insufficient sleep, and irregular sleep would contribute to worse outcomes on the three key outcome variables.

2.9. Data analysis

SRI scores were calculated using a custom script for MatLab Version R2017b. MatLab Version R2017b was also used for the path analysis, using a customized version of the PLS-SEM Toolbox. SPSS Statistics Version 20.0 (IBM, Armonk, New York) was used for all other data analysis. Data are expressed as mean ± standard deviation (SD) unless otherwise stated. Independent samples t-tests were performed for comparison of continuous variables between phenotypes. For dichotomous variables (MEQ, ESS, Sheehan Disability Scale subscales), chi-square analysis was performed for comparison between phenotypes. As SRI scores are not normally distributed, a Mann–Whitney U test was performed to compare SRI score between phenotypes and effect sizes were determined using η^2. Direct associations between SRI and the outcome variables were examined using Pearson correlations. Significance level was set at 0.05 for all statistical analyses.

2.10. Data retention

Data were collected for 185 participants; however, 15 (8.1%) participants were excluded due to; missing actigraphy data (n = 7, 3.8%), unable to calculate DLMO (n = 3, 1.6%), and five participants (2.7%) were excluded because they had fewer than the four days of actigraphy data required to calculate an SRI score. Therefore, the final analysis was based on N = 170 participants.

3. Results

3.1. Participants and outcome measures

Participants (N = 170) were aged 29.8 ± 10.7 years and a BMI of 24.8 ± 4.1 kg/m^2 (Table 1). Average DLMO clock-time for the whole group was 22:07 ± 1:29 h (range: 18:42–02:24). The circadian group had an average DLMO clock-time of 22:50 ± 1:23, and the non-circadian had an average DLMO clock-time of 21:17 ± 1:07. For the whole group, the average DBT-DLMO phase angle was 0.37 ± 1.38 before desired bedtime (range: 4.10 before to 3.22 h after DBT). For the circadian group, the average DBT-DLMO phase angle was 0.63 ± 0.90 h after DBT (range: 0.50 h before to 3.22 h after DBT). For the non-circadian group, average DBT-DLMO phase angle was 1.53 ± 0.82 h before DBT (range: 0.53–4.10 h before DBT). There were no differences between circadian and non-circadian groups for sex, age, BMI, or total sleep time ($p > 0.05$). Mean SRI was 79.4 ± 11.5 (range: 27.9 to 96.6). The circadian group (SRI = 77.8 ± 12.0) had less regular sleep patterns than the non-circadian group (SRI = 81.2 ± 10.8), although the effect size for this difference was small ($p < 0.05$, $\eta^2 = 0.03$). The circadian group also had later DLMO time ($p < 0.001$), bedtime ($p = 0.02$), sleep onset time ($p = 0.009$), wake time ($p < 0.001$), than the non-circadian group. For functional and mood outcomes, the circadian group scored significantly worse for depression (BDI-II, $p = 0.02$), daytime sleepiness (ESS, $p = 0.02$), and sleep related impairments (PROMIS, $p = 0.02$) (Table 1). There were no differences between groups for anxiety or symptom severity (ISI).

3.2. Associations of SRI with other sleep/circadian variables

There was a significant negative correlation between DLMO and SRI ($r = -0.28$, $p < 0.001$), indicating that individuals with more delayed DLMO tended to have less regular sleep patterns (Fig. 1A). There were also significant negative correlations between SRI and

Table 1
Participant characteristics, sleep and circadian timing, mood, daytime functioning and symptom severity measures for the whole sample (N = 170) and circadian (n = 91) and non-circadian DSWPD groups (n = 79).

	Total	Circadian	Non-circadian	p[b]	Effect Size
Demographics					
N	170	91	79		–
Sex n (%)	79 (46.5) M, 91 (53.5) F	38 (41.8) M, 53 (58.2) F	41 (51.9) M, 38 (48.1) F	0.22	–
Age (years)	29.75 ± 10.71	28.37 ± 9.85	31.34 ± 11.47	0.07	–
BMI (kg/m^2)	24.78 ± 4.06	24.99 ± 4.44	24.53 ± 3.59	0.46	–
cMEQ	24.67 ± 5.11	24.10 ± 4.89	25.32 ± 5.30	0.12	–
Moderately Evening n (%)	24 (14.1)	9 (9.9)	15 (19.0)	0.09	–
Definitely Evening n (%)	146 (85.9)	82 (90.1)	64 (81.0)		
No. work days	4.54 ± 1.30	4.35 ± 1.41	4.76 ± 1.14	**0.04**	–
Sleep & circadian timing[c]					
SRI Score	79.40 ± 11.54	77.80 ± 11.99	81.24 ± 10.77	**0.04**[a]	0.30
Dim Light Melatonin Onset (HH:MM)	22:07 ± 1:29	22:50 ± 1:23	21:17 ± 1:07	**<0.001**	1.23
DBT-DLMO Phase Angle Difference (hours)	−0.37 ± 1.38	0.63 ± 0.90	−1.53 ± 0.82	**<0.001**	2.51
Total Sleep Time (hours)	6.65 ± 0.81	6.72 ± 0.73	6.57 ± 0.89	0.25	0.18
Bedtime (HH:MM)	00.41 ± 1:18	00:53 ± 1:16	00:26 ± 1:17	**0.02**	0.35
Sleep Onset Time (HH:MM)	01:01 ± 1:17	01:16 ± 1:17	00:44 ± 1:14	**0.009**	0.43
Wake Time (HH:MM)	8:43 ± 1:17	9:02 ± 1:19	8:21 ± 1:09	**<0.001**	0.55
Midsleep Time (HH:MM)	04:52 ± 1:13	05:09 ± 1:14	04:32 ± 1:06	**0.001**	0.53
Mood and functional outcomes					
BAI	7.09 ± 6.26	7.52 ± 6.74	6.58 ± 5.64	0.34	0.15
BDI-II	9.05 ± 8.87	10.43 ± 10.53	7.43 ± 6.10	**0.02**	0.35
PROMIS Sleep related impairments	25.61 ± 7.58	26.92 ± 7.19	24.10 ± 7.77	**0.02**	0.38
ESS	5.76 ± 3.83	6.42 ± 3.88	5.00 ± 3.64	**0.02**	0.38
Normal (≤10) n (%)	148 (87.1)	77 (84.6)	71 (89.9)	0.31	
Excessive daytime sleepiness (>10) n (%)	22 (12.9)	14 (15.4)	8 (10.1)		
Sheehan Disability Scale	14.81 ± 5.54	15.22 ± 5.08	14.3 ± 6.03	0.30	0.17
Impairment to Work/school	6.06 ± 2.17	6.31 ± 1.94	5.77 ± 2.39	0.11	0.25
Not impaired (≤5) n (%)	65 (38.2)	30 (33.0)	35 (44.3)	0.13	
Impaired (>5) n (%)	105 (61.8)	61 (67.0)	44 (55.7)		
Impairment to social life	4.10 ± 2.41	4.14 ± 2.42	4.04 ± 2.41	0.78	0.04
Not impaired (≤5) n (%)	121 (71.2)	67 (73.6)	54 (68.4)	0.45	
Impaired (>5) n (%)	49 (28.8)	24 (26.4)	25 (31.6)		
Impairment to family life	4.74 ± 2.47	4.77 ± 2.53	4.71 ± 2.41	0.89	0.02
Not impaired (≤5) n (%)	103 (60.6)	57 (62.6)	46 (58.2)	0.56	
Impaired (>5) n (%)	67 (39.4)	34 (37.4)	33 (41.8)		
Absenteeism	2.65 ± 4.08	3.13 ± 4.41	2.09 ± 3.61	0.10	0.26
Presenteeism	9.46 ± 7.11	10.20 ± 7.23	8.58 ± 6.90	0.14	0.23
Symptom severity					
Insomnia Severity Index	12.52 ± 5.05	12.78 ± 4.69	12.21 ± 5.44	0.46	0.11

Bold values indicate p values less than 0.05.
BMI = , cMEQ = , SRI = , BAI = , BDI-II = , PROMIS = , ESS = , Data is represented as mean ± SD.
[a] p value for Mann–Whitney U.
[b] =p value for comparison between Circadian and Non-circadian phenotypes.
[c] All sleep variables are calculated from actigraphy, averaged over seven days, unless otherwise stated; Effect size reported as Cohen's *d* (0.2 = small effect size, 0.5 = medium effect size, and 0.8 = large effect size.

bedtime ($r = -0.43$, $p < 0.001$, Fig. 1B), sleep onset time ($r = -0.44$, $p < 0.001$, Fig. 1C), midsleep time ($r = -0.40$, $p < 0.001$, Fig. 1D), and wake time ($r = -0.32$, $p < 0.001$, Fig. 1E). Total sleep time correlated positively with SRI ($r = 0.17$, $p < 0.05$, Fig. 1F), indicating that individuals with more regular sleep tended to sleep longer. There were no significant correlations between SRI score and sleep onset latency, wake after sleep onset, or sleep efficiency, with r values of 0.02, 0.01, and 0.01 ($p > 0.05$), respectively.

3.3. Associations of SRI with daytime function, sleep-related impairment, mood, and symptom severity

Associations were investigated between SRI and outcome measures reflecting daytime function, sleep-related impairment, mood, and symptom severity. As shown in Table 2, all outcome variables trended towards a negative correlation with SRI, except impairment to social life ($r > 0$), but only two of these relationships were significant: Impairment to work/school ($p < 0.05$) and Absenteeism ($p < 0.001$).

Table 2
Correlations between SRI and daytime function, sleep-related impairment, mood and symptom severity outcomes.

	r	p
Daytime Function		
Work/School	−0.17	**0.03**
Social Life	0.003	0.97
Family Life	−0.07	0.41
Absenteeism	−0.32	**<0.001**
Presenteeism	−0.12	0.11
Sleep-Related Impairment		
ESS	−0.34	0.12
PROMIS Sleep related impairment	−0.27	0.34
Mood		
BDI-II	−0.32	0.20
BAI	−0.33	0.17
Symptom Severity		
ISI	−0.36	0.10

Bold values indicate p values less than 0.05.

3.4. Comparison of relationships between SRI and outcome measures between phenotypes

Overall, the relationships between SRI and the outcome measures were similar between the groups and this was reflected in the separate associations. There were no significant differences between groups for the association between SRI and bedtime, sleep onset time, midsleep time or wake time ($p > 0.05$). There was, however, a significant difference between the groups for total sleep time and SRI. The relationship between SRI and total sleep time was not significant for the circadian group ($r = 0.02$, $p > 0.05$), whereas there was a highly significant positive correlation for the non-circadian phenotype ($r = 0.38$, $p < 0.001$), indicating that increased sleep regularity is associated with increased total sleep time. There were no significant differences between groups in the associations between SRI and depression, anxiety, daytime sleepiness, sleep-related impairments or symptom severity ($p > 0.05$).

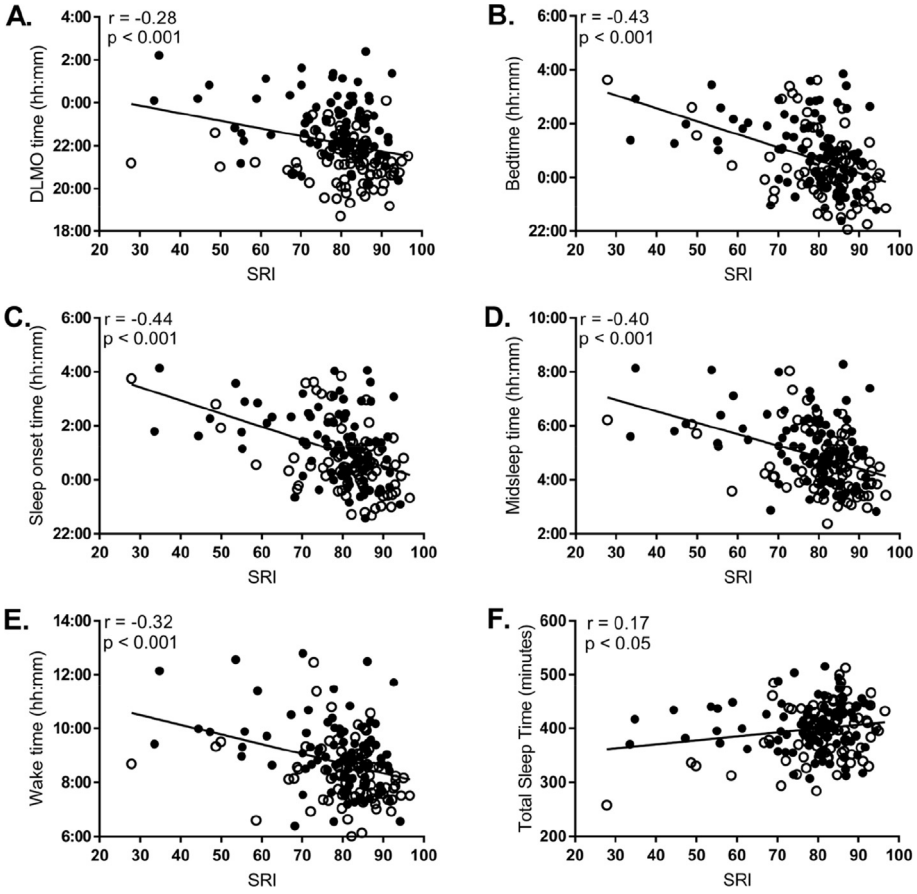

Fig. 1. Direct associations between SRI and timing of DLMO, sleep and wake. Closed circles = DSWPD Circadian phenotype, open circles = DSWPD Non-circadian phenotype. Later clock times for DLMO time (A), bedtime (B), sleep onset time (C), midsleep time (D), wake time (E) were associated with reduced regularity. Shorter total sleep time (F) was associated with decreased regularity.

3.5. Path analysis

The path analysis in Fig. 2 showed that total sleep time had direct associations with both phase angle and sleep onset time, but no direct association with SRI. This finding suggests that the significant bivariate correlation between SRI and total sleep time reported above is confounded by sleep onset time and phase angle, whereby sleep onset time and phase angle influence the relationship between SRI and total sleep time. As such, we were able to exclude total sleep time as a potential driver of the model. We considered two plausible hypotheses for the directional relationship between sleep onset time and SRI. The primary hypothesis was that later sleep onset time could decrease sleep regularity (lower SRI). Moreover, delaying sleep could result in sleep curtailment due to morning events on some days of the week (eg, work days) and not others (eg, free days), leading to irregular sleep patterns. The alternative hypothesis was that lower SRI could drive later sleep onset time: irregular sleep could lead to greater light exposure in the phase delay region of the light phase response curve, causing circadian delay [50,51], in turn delaying sleep onset times. The latter hypothesis was rejected in this instance due to the finding that there was no significant direct association between SRI and phase angle in the path model; the association between these variables was mediated by sleep onset time. Consequently, we chose sleep onset time driving SRI as the most plausible directionality of effect in our path model.

Fig. 3A shows the path analysis for daytime function (Sheehan Disability Scale- Absenteeism subscale). No direct association was found between sleep onset time and Absenteeism, although SRI significantly mediated the relationship via a weak direct association ($\beta = -0.23$, $p < 0.01$). Phase angle had a weak direct positive association with Absenteeism ($\beta = 0.16$, $p < 0.05$), with a weaker total indirect association across all mediation paths ($\beta = 0.10$). Total sleep time had no relationship with Absenteeism ($\beta = 0.001$).

Fig. 3B shows the path model for sleep-related impairment (ESS). Total sleep time had the strongest direct association with ESS ($\beta = -0.24$, $p < 0.01$). Phase angle had a weak but significant direct association with ESS ($\beta = 0.14$, $p < 0.05$); the net indirect association across all mediation paths was close to zero ($\beta = 0.04$) due to opposing positive and negative indirect associations via sleep onset time and total sleep time, respectively. Sleep onset time and SRI did not have significant direct associations with ESS.

Fig. 3C shows the path model for mood (BDI). Phase angle had a weak but significant direct association with BDI ($\beta = 0.16$, $p < 0.05$). Direct paths from all other sleep and circadian variables to BDI were weak and non-significant.

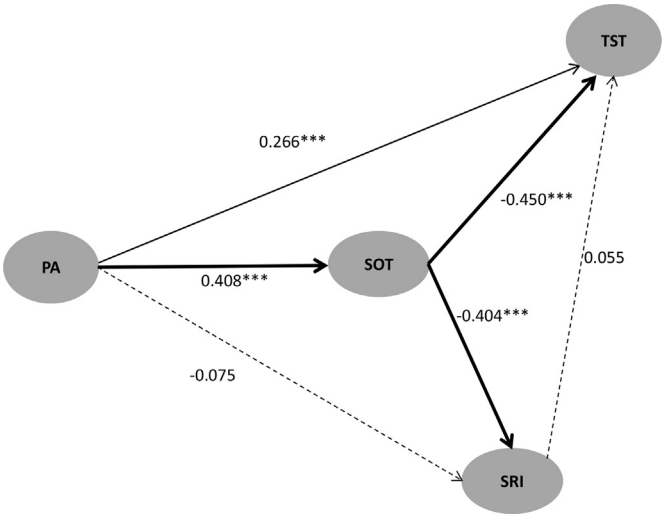

Fig. 2. Path model illustrating indirect effects of DBT-DLMO phase angle difference (PA) on variability (SRI) through the mediator of sleep onset time (SOT). Arrows are labeled with standardized β values. Solid lines indicate statistically significant direct effect paths and dotted lines indicate effect paths that are not significant. The width of the solid lines is proportional to the standardized β value. Significance is indicated by: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

4. Discussion

Previously, have established that misalignment between circadian phase and sleep contributes significantly to the etiology, symptoms, and symptom severity of DSWPD [35]. The current study aimed to characterize sleep regularity in a DSWPD population and examine the relationships between SRI and habitual sleep and wake timing, DBT-DLMO phase angle, mood, and functional outcomes. We demonstrated that decreased sleep regularity is significantly associated with later habitual sleep-wake timing and later DLMO. We also showed a significant positive relationship between total sleep time and sleep regularity. This differs from the relationship in college students, where there is no relationship between total sleep time and sleep regularity [22]. This is likely because college students are far more likely to nap during the day [52], allowing them to catch up on lost nighttime sleep. Alternately, our population consisted of day-workers for whom this strategy would not typically be available. DBT-DLMO phase angle emerged as the only variable to directly associate with all three outcomes, even after including mediation by other variables. In addition to our previous findings [35], this provides further evidence that objectively measured circadian timing and phase angle is vital as a diagnostic measure in the DSWPD population. Of note, sleep onset time did not directly associate with any of the key outcomes in our path models, demonstrating that delayed sleep *per se* is not necessarily a driver of poor outcomes, nor a reliable marker of circadian disruption. To summarise, delayed sleep appears to be problematic only when it leads to sleep curtailment, irregular sleep, or sleep occurring at inappropriate circadian phases.

We found that irregular sleep mediates the effects of delayed sleep onset time on daytime function, while reduced total sleep time mediates the effects of delayed sleep on sleep-related impairment (daytime sleepiness). Absenteeism showed a significant strong negative relationship with sleep regularity and path analysis confirmed that this association was not simply mediated by other variables. Previous research has indeed shown that individuals at high risk of DSWPD are significantly more likely to report frequent absenteeism from work or school [53]. The findings of this study indicate that irregular sleep timing plays a role in the manifestation and/or the maintenance of the overt detrimental consequences, particularly daytime function, in DSWPD. Further, the irregular sleep timing observed in patients with DSWPD potentially perpetuates the inability to sleep at an appropriate circadian phase due to the large night-to-night changes in bed and sleep onset times, thereby impacting sleep quality and quantity [54], which has subsequent consequences for daytime function.

The path analyses we conducted led us to conclude that the relationship between phase angle and SRI is most likely mediated by sleep onset time. However, these relationships could also be bidirectional, with irregular sleep being potentially a driver of greater misalignment of circadian phase. The circadian group was more variable in sleep timing, and also showed significantly later sleep onset time and circadian timing compared to the non-circadian group. Although the current study did not examine variability in circadian timing, these results complement a recent study, in which there was greater variability in sleep timing and DLMO in DSWPD than controls [55]. The authors surmised that

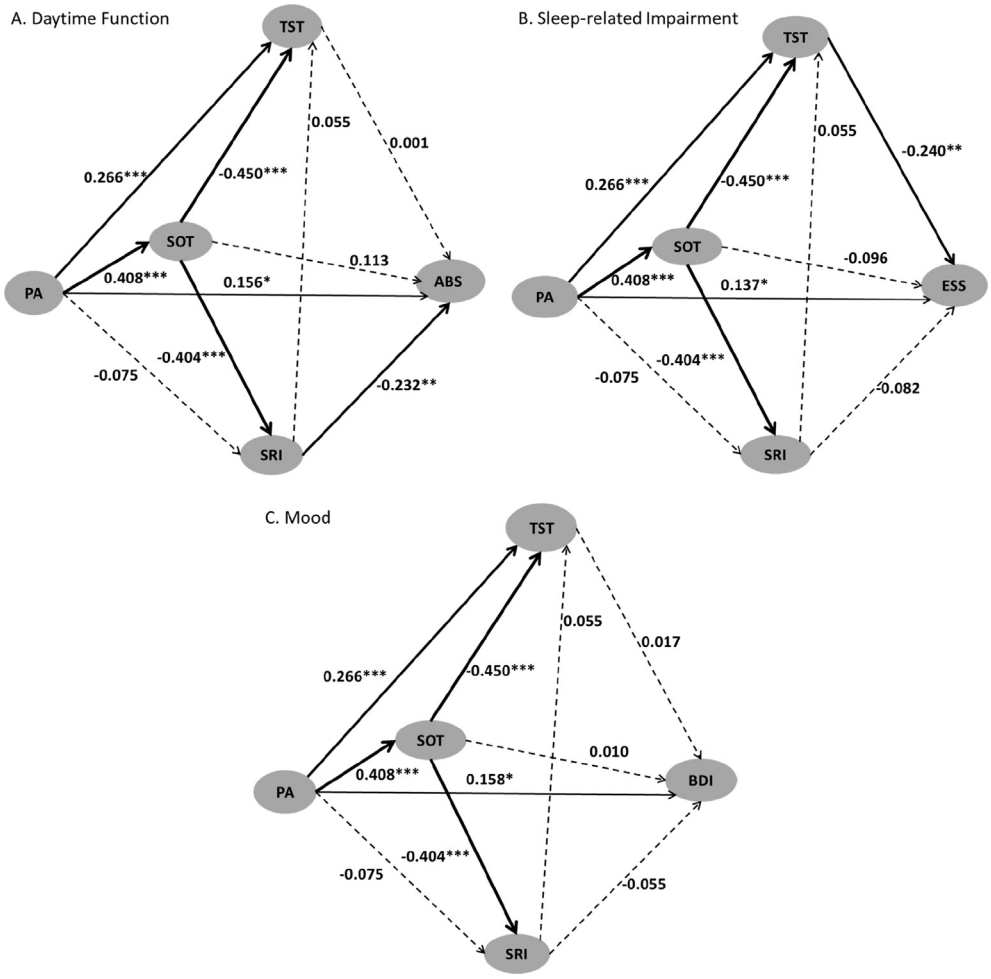

Fig. 3. Path models showing the mediating effect of variability (SRI) on daytime function (Absenteeism [ABS]; panel A), Sleep-related impairment (ESS; panel B), and Mood (BDI-II; panel C). Arrows are labeled with standardized β values. Solid lines indicate statistically significant direct effect paths and dotted lines indicate effect paths that are not significant. The width of the solid lines is proportional to the standardized β value. Significance is indicated by: * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

variability in DLMO time is potentially mediated by sleep variability, presumably via changes in the pattern of light–dark exposure, which is gated by sleep [56]. We found that total sleep time is only significantly associated with sleep regularity for the non-circadian phenotype. This suggests that night-to-night variability in sleep timing is likely driven by behavioral choices, and the resultant light exposure, rather than being precipitated directly by the underlying circadian physiology.

We did not find any association between sleep regularity and mood, whereas previous research in a non-clinical sample has found sleep regularity to be predictive of daily mood [31]. Instead, we found a direct relationship between phase angle and mood, consistent with our finding of a very strong relationship between phase angle and risk of depression in this group [35]. Circadian misalignment, particularly as observed in DSWPD, is strongly associated with depression [57–59]. Whilst it is likely that irregular sleep timing perpetuates circadian misalignment, it does not appear to directly influence mood. SRI may capture different aspects of regularity than those that have the greatest impact on mood. For example, previous research has demonstrated that variability of sleep duration in particular, rather than timing, is related to depression [60]. Several studies investigating variability in sleep duration found that night-to-night variability in both actigraphically measured [24,61] and self-report [24] sleep duration was significantly associated with increased depressive symptom severity. Similar findings were reported for insomnia patients, where increased variability of sleep duration was significantly associated with increased depressive symptoms [62]. Nonetheless, further research investigating the link between mood outcomes and other dimensions of variability in sleep, such as sleep duration, sleep onset latency, and wake after sleep onset, is warranted in this population.

One notable limitation in this study is the short recording duration for the sleep and wake information (seven days). Ideally, sleep regularity would be assessed across multiple weeks. We note that our sample was heterogeneous in the number and distribution of work and free days within the recording period, which reduced the likelihood of any day-of-week bias contributing to the results. An additional limitation posed by a short actigraphy recording period is the potential for mis-identification of patients with other circadian rhythm sleep disorders, such as Non-24-h Sleep-Wake Disorder (N24SWD). Typically, extended periods of actigraphy recording are necessary to determine whether an individual is entrained to the 24-h day.

In addition to characterizing sleep regularity in a DSWPD population, this study has reiterated our previous findings that measuring circadian phase is important for diagnosis and treatment, given the strong association between circadian misalignment and detrimental outcomes for mood and daytime function. Moreover, the findings of the current study indicate that sleep regularity

is a part of the symptomology that should be considered in the diagnosis and treatment of DSWPD, particularly as it is likely a perpetuating factor for the disorder; and, if not addressed, may undermine treatment approaches. Although diagnostic criteria require measurement of sleep on both weekdays and weekends, bed and wake times are averaged within weekdays and within weekends to quantify social jetlag while overlooking all other sources of day-to-day variability. Acknowledging the night-to-night variability in sleep during diagnosis may also allow clinicians to provide better education to their patients about the importance of maintaining a regular sleep schedule. Finally, measuring and considering sleep regularity provides a possible key indicator of symptom improvement following implementation of treatment.

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Conflicts of interest

Ms Murray has served as a Project Leader in the Cooperative Research Centre for Alertness, Safety and Productivity.

Dr Phillips serves as a Project Investigator in the Cooperative Research Centre for Alertness, Safety and Productivity.

Dr Magee serves as a Project Leader in the Cooperative Research Centre for Alertness, Safety and Productivity.

Dr Sletten reports her institution has received equipment donations or other support from Philips Lighting, Philips Respironics, Optalert and Compumedics. Dr Sletten serves as a Project Leader in the Cooperative Research Centre for Alertness, Safety and Productivity.

Dr Gordon serves as a Project Leader in the Cooperative Research Centre for Alertness, Safety and Productivity.

Dr Lovato reports no conflicts of interest.

Dr Bei reports no conflicts of interest.

Dr Bartlett reports no conflicts of interest.

Dr Kennaway reports no conflicts of interest.

Dr Lack is shareholder in Re-Time Pty Ltd.

Dr Grunstein is a Program Leader for the Cooperative Research Centre for Alertness, Safety and Productivity. He has served on local advisory boards for Merck and Teva and has been a medico-legal expert witness for Queensland Health, NSW Nurses Federation, NSW Health and NSW Director of Public Prosecutions.

Dr Lockley declares no conflicts with the work described herein. In the past three years, he has received consulting fees from the Atlanta Falcons, Atlanta Hawks, Consumer Sleep Solutions, OpTerra Energy Services Inc., Pegasus Capital Advisors LP, Serrado Capital, Slingshot Insights, and Team C Racing, and has current consulting contracts with Akili Interactive, Apex 2100 Ltd, Delos Living LLC, Headwaters Inc., Hintsa Performance AG, Light Cognitive, Lighting Science Group Corporation, Mental Workout, PlanLED, Six Senses and Wyle Integrated Science and Engineering. S.W.L. has received unrestricted equipment gifts from Biological Illuminations LLC, Bionetics Corporation, and F.Lux Software LLC; has equity in iSLEEP, Pty; advance author payment and/or royalties from Oxford University Press; honoraria plus travel, accommodation and/or meals for invited seminars, conference presentations or teaching from BHP Billiton, Lightfair, Informa Exhibitions (USGBC), Teague; travel, accommodation and/or meals only (no honoraria) for invited seminars, conference presentations or teaching from DIN, FASEB, Lightfair, SLTBR, and USGBC. S.W.L. has completed an investigator-initiated research grant from Biological Illumination LLC and has an ongoing investigator initiated grant from F. Lux Software LLC. S.W.L. holds a process patent for “Systems and methods for determining and/or controlling sleep quality,” which is assigned to the Brigham and Women's Hospital per Hospital policy. S.W.L. has also served as a paid expert for legal proceedings related to light, sleep, and health. S.W.L. is a Program Leader for the CRC for Alertness, Safety and Productivity, Australia.

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