Cognitive performance in DSWPD patients upon awakening from habitual sleep compared to forced conventional sleep.

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Summary

Difficult early morning awakening is one of the defining symptoms of delayed sleep-wake phase disorder (DSWPD). It is accompanied by low cognitive arousal and drowsiness resulting in difficulty concentrating and focusing attention upon awakening. We designed the current study to quantitate cognitive performance (i.e. omissions, commissions, reaction time (average and variability), and cognitive domains (i.e. focused attention, sustained attention, impulsivity and vigilance) with Conners' Continuous Performance Test II (CCPT-II) during both habitual and conventional (0000-0700) sleep-wake schedule in young adult DSWPD-patients (n = 20, mean age = 24.8, SD = 3.0) and controls (n = 16, mean age = 24.4, SD = 3.4). The CCPT-II was administered after awakening and in the afternoon during both habitual and conventional conditions. In-laboratory polysomnography was performed for two nights. We assessed sleep, tiredness, chronotype and depression by questionnaires. Saliva was sampled for dim light melatonin onset measurements. Repeated measures ANOVAs were applied for the CCPT-II measures with group (patient/control), time (afternoon/morning) and condition (habitual/conventional schedule) as fixed factors. DSWPD-patients had reduced reaction times, especially in the morning, greater response speed variability, and made more omission and commission errors compared to controls. DSWPD-patients also had reduced focused attention, especially upon forced early awakening. DSWPD-patients' short total sleep time could not statistically explain this outcome. In conclusion, we observed a state-dependent reduced ability to focus attention upon early morning awakening in DSWPD patients. Patients also had more omissions, longer reaction time (RT), and increased RT-variability after habitual sleep, suggesting a possible small cognitive trait dysfunction in DSWPD.

Introduction

The hallmark of delayed sleep-wake phase disorder (DSWPD) is a significant delay in the phase of the major sleep episode, manifested as inability to fall asleep and wake up at conventional bed and rise times (ICSD 3rd edition) (American Academy of Sleep Medicine, 2014). Associated features like concentration difficulties, depression, and anxiety have also been reported (American Psychiatric Association, 2013, Kripke et al., 2008, Abe et al., 2011), but it is the extreme difficulty in morning awakening and the inability to function normally during the early morning hours that cause the DSWPD-patients' social and work-related problems (American Psychiatric Association, 2013).

This transient state of low cognitive arousal and confusion upon forced awakening in DSWPD seems to be an excessive form of sleep inertia (SI) as a result of curtailed sleep time and waking up from a circadian time of high sleep propensity (Tassi and Muzet, 2000, Marzano et al., 2011). It is *assumed* that DSWPD patients have normal cognitive performance upon waking from habitual sleep with normal duration and awakening at the appropriate circadian time for the individual (American Academy of Sleep Medicine, 2014). This is supported by a study showing the degree of SI to be related to chronotype, with evening-type individuals reporting greater effects of SI upon early awakening (work days), but not during habitual sleep-wake schedule (weekends) (Roenneberg et al., 2003). Moreover, several studies have demonstrated similar performance differences between morning and evening chronotypes, where morning-type individuals perform better in the morning and evening-type individuals perform better in the afternoon in a range of cognitive abilities (Ritchie et al., 2017, Lara et al., 2014, Schmidt et al., 2007). However, there have been very few empirical investigations of specific cognitive performance changes after forced morning awakening in patients diagnosed with DSWPD.

In a previous controlled study, we found that reaction times on the Conner's Continuous Performance Test II (CCPT-II) became significantly slower upon forced early awakening compared to performance during the afternoon in DSWPD (Solheim et al., 2014), but this study was limited by a small sample size (n=18) and not having a night of habitual sleep to compare against. Moreover, the CCPT-II is particularly relevant as it measures several aspects of performance over time, and has a factor structure that reflects independent cognitive domains like focused attention, sustained attention, vigilance and impulsivity (Egeland, 2007, Egeland and Kovalik-Gran, 2010a). Many of these abilities would relate to real-world behaviors (e.g., driving), yet no studies have investigated these aforementioned domains previously in DSWPD. Thus, in the present study we wanted to replicate and expand this previous study in a new sample of DSWPD patients.

The principal aim of the current study was to test DSWPD patients' cognitive performance upon awakening from a night of habitual (self-chosen) sleep-wake schedule compared to performance upon forced early morning awakening following a conventional sleep-wake schedule and to compare their performance patterns to healthy controls. We hypothesized that (i) the DSWPD group would exhibit worse cognitive performance than controls as measured by CCPT-II primary variables (omission, commission, reaction time [average and variability]) and supplementary cognitive domain variables (focused attention, sustained attention, vigilance, impulsivity), and that (ii) this effect would be evident after forced early morning awakening, and not after awakening from habitual sleep. A secondary aim was to explore the correlation between subjective tiredness and cognitive performance.

Methods

Participants

DSWPD patients were recruited from the Østmarka Sleep Clinic's waiting-list and by general advertisement on the Norwegian University of Science and Technology webpage, local campuses and a local newspaper. To be included, the patients had to meet the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV 307.45) diagnostic criteria for circadian rhythm sleep disorder (American Psychiatric Association, 1994) and the ICSD-3 criteria A-E for DSWPD (American Academy of Sleep Medicine, 2014). All patients completed a 14-day sleep diary prior to a diagnostic interview at the Østmarka Sleep Clinic at St. Olavs University Hospital, Trondheim, Norway. An experienced psychiatrist (20 years of general clinical experience and 13 years of clinical experience specifically with DSWPD) performed the diagnostic interview and the diagnostic assessments. The semi-structured diagnostic interview developed at the Østmarka Sleep Clinic covers: current sleep pattern, daytime sleepiness, how the sleep disturbance developed and has presented itself to current date, current or past treatment attempts, current and past substance or alcohol use, sleep hygiene, current medications, known somatic conditions, screening for organic sleep disorders (restless legs, periodic limb movements, sleep apnea, parasomnias, hypersomnia), screening for mental disorders, description of circadian rhythm and delayed sleep phase, and finally whether the patients met all diagnostic criteria for DSWPD. If there was uncertainty about the diagnosis, the sleep diaries and patient's sleep history were discussed with a clinical psychologist before final inclusion. We used the SCID-I screening items for mental disorders in addition to the clinical impression from the interview.

Twenty patients and sixteen healthy age-matched controls were included in the study (Table 1). All control participants had a normal circadian rhythm (i.e., bedtime 2300-2400 h; wake-up time 0700-0800 h) and were otherwise healthy (applying the same exclusion criteria as for patients). Exclusion criteria were: other sleep disorders, migraine, infections, cancer, neurological disorders, schizophrenia, other psychotic disorders, bipolar disorder, substance-

related disorders, obsessive compulsive disorder, attention-deficit hyperactivity disorder, heart and lung disease, brain or cochlear implants, pregnancy/breastfeeding and daily use of sleep-disturbing medications the last 4 weeks. We did not use the BDI- questionnaire for exclusion, because individuals with DSWPD often display increased levels of depressive symptoms without meeting formal diagnostic criteria of a depressive episode. Only norepinephrine-dopamine or serotonin reuptake inhibitors were allowed during inclusion (bupropion had been prescribed for 1 patient). All subjects were also asked for current drug use on the first study day (one patient used NSAIDs, one control used antihistamines for seasonal allergy).

The study protocol was approved by the Regional Committees for Medical and Health Research Ethics (2011/1406). All participants provided written informed consent.

Procedure

On Monday, participants from both groups came to St. Olavs Hospitals sleep laboratory at 1400 h to have polysomnographic equipment applied by an experienced technician. Participants slept at home and followed their preferred sleep-wake schedule (Figure 1). The first night of polysomnography (PSG) was an adaptation night. We did not observe any breathing (apnea hypopnea index<5/h) or movement (periodic limb movement index<15/h) problems during the subsequent analysis.

Participants arrived on Tuesday at 1400 h to be prepared for a second polysomnography. At 1500 h, the baseline cognitive test was administered. All participants also completed several questionnaires during the evening (see Self-Report Measures below). Saliva for dim light melatonin onset (DLMO) was sampled hourly from 1900 h until self-determined bedtime. Earliest bedtime was set to 2300 h and latest bedtime was set to 0400 h to ensure at least an 8-hour sleep opportunity. Participants who did not wake up by 1200 h were awakened by the

researcher. For practical reasons we had to terminate sleeping at 1200 h because the lab was not available after 1300 h. In order to ensure a 'normal'8 hour sleeping-opportunity they were accordingly not allowed bedtime later than 0400 h.
The second administration of the cognitive test was performed upon awakening from habitual sleep. Subject slept at home Wednesday night.

Thursday (the second night spent at the sleep laboratory), participants again came for a PSG mounting at 1400 h. The third administration of the cognitive test was performed at 1500 h following PSG mounting. Bedtime was scheduled for 0000 h. A PC-based alarm clock was activated at 0700 h on Friday morning. The fourth and final administration of the cognitive test was performed upon awakening (between 0706 and 0710 h, depending on the time required to wake up the participant).

Conners' Cognitive Performance Test II (CCPT II)

Participants were placed in front of a computer screen, and were told to respond by pressing the space bar on a keyboard every time a letter A-Z (target) appeared on the screen, and to withhold their response whenever the letter X (non-target) appeared (Homack and Riccio, 2006). The participants were told to respond as quickly and accurate as possible. All together there were 324 targets and 36 non-targets (10%). The letters appeared on the screen for 250 milliseconds and in varying inter-stimulus intervals of either 1, 2 or 4 seconds. The test took 14 minutes to complete. Four primary dependent variables from the CCPT-II were examined to evaluate response speed, accuracy, and consistency: omissions (failure to respond to targets), commissions (responses to non-targets), Hit RT (average reaction time for correct responses), Hit RT STE (Standard Error reflecting response speed variability). These four primary variables are most commonly used as a measure of response speed and accuracy and

were thus used to test our hypotheses (Homack and Riccio, 2006, Wilhelmsen-Langeland et al., 2013).

Cognitive domains

Based on factor analysis by Egeland et al. (Egeland, 2007, Egeland and Kovalik-Gran, 2010a), we calculated four supplementary cognitive domain variables as averages from selected primary CCPT-II T-scores. The change in performance over the six consecutive blocks and some interstimulus interval (ISI) change variables were also included. A minor modification compared to the original domains was that change-scores for omissions and commissions were not included as no standardized scores (T-scores) are provided for these in the CCPT-II software. Consequently, we did not compute the Change in Control domain. As only the delta commissions measure loads heavily on the fifth domain (Change in Control), this domain seems to have a weak factor structure and has limited value beyond this single measure (Egeland and Kovalik-Gran, 2010a, Egeland and Kovalik-Gran, 2010b). The included domain variables were: Focused Attention = average of Variability, Hit RT SEM, Perseverations and Omissions; Impulsivity = average of 100-Hit RT and Commissions; Sustained Attention = average of Hit RT Block-Change and Hit RT SEM Block-Change; and Vigilance = average of Hit RT ISI Change and Hit RT SEM ISI Change (Egeland, 2007, Egeland and Kovalik-Gran, 2010a).

Polysomnography

A standard PSG-montage was used in accordance with the international 10-20 system and AASM technical recommendations, and sleep was scored according to the AASM manual version 2.0 in order to have exact measures of total sleep time (TST) (Silber et al., 2007). Electroencephalography (EEG) included electrodes F3, F4, C3, C4, O1, O2, A1, A2 with Cz as reference. Electrooculography (EOG) included one electrode placed 1 cm over and 1 cm

lateral to the right lateral canthus and one electrode placed 1 cm under and 1 cm lateral to the left lateral canthus. Electromyography (EMG) electrodes were placed on the chin. A nasal airflow sensor and an oronasal thermistor monitored nasal flow, pressure and airflow. An infrared O_2-sensor was placed on the index finger.

Self- reported measures

Subjective level of tiredness 2 minutes before CCPT-II test: On Tuesday and Thursday afternoon, as well as Wednesday and Friday morning immediately upon awakening, patients were asked to report their subjective level of tiredness on a numeric rating scale (NRS) from 0 to 100 where 0 = not tired at all and 100 = could fall asleep within the next minute.

Insomnia symptoms: Scores for difficulty falling asleep for the last three months were obtained from Karolinska sleep questionnaire, where 0 = never, 1 = a few times per year, 2 = a few times a month, 3 = several times per week and 4 = daily (Akerstedt and Gillberg, 1990).

Horne–Östberg Morningness Eveningness Questionnaire (MEQ): The MEQ is a 19-item questionnaire assessing level of diurnal preference. The cut-off values are ≤ 41 = evening type; 42-58 = intermediate; ≥ 59 morning type (Horne and Ostberg, 1976). DSWPD symptoms correspond to an extreme evening-type.

Beck Depression Inventory (BDI): The BDI is a 21-item self-report measure of behavioral, cognitive and affective symptoms associated with clinical depression. The cut-off values are: 0-9 = normal; 10-18 = mild; 19-29 = moderate; and ≥ 30 = severe depression (Beck et al., 1988).

Dim light melatonin onset (DLMO)

Food or beverage consumption was not allowed 30 minutes prior to each saliva sample taking. Samples were taken hourly between 1900 h and bedtime. Saliva was collected using the Bühlmann Salivette ® collection kit (Bühlmann Laboratories AG, Schönenbuch, Switzerland). Instructions provided by the manufacturer were followed. Participants were asked to chew on the provided swab for a minimum of 1-2 minutes. Caffeinated drinks were not consumed on the evening of saliva collection. Certain foods were avoided, such as bananas, chocolate, milk and almonds. Samples were immediately stored in a refrigerator at 4 °C. The samples were analyzed using the Bühlmann Direct Saliva Melatonin ELISA kit. Dim light melatonin onset (DLMO) was defined as the time at which melatonin concentration reached a 4 pg/ml threshold (Keijzer et al., 2011, Rahman et al., 2009).

Data analysis:

We used the Mann-Whitney U test as a descriptive tool for group differences in demographic, clinical and polysomnographic variables. Spearman correlation explored the association between subjective tiredness and cognitive performance. CCPT-II variables were natural logarithmic (LN) transformed for the statistical analysis. We had no missing data and a simple categorical repeated model, hence repeated measures analysis of variance (ANOVA) were applied for the four primary and the four cognitive domain CCPT-II measures with group (patients/controls), time (afternoon/morning) and condition (habitual/forced schedule) as fixed factors. Two sets of secondary repeated measures analysis of covariance (ANCOVA) were also conducted (one for the forced pair, another for the habitual pair) to control for total sleep time (TST). Effect size estimates were reported as eta-squared (η^2). The power to detect an effect = 0.96 SD, based on a two-sample Student's t-test, was 80 %. We did not apply corrections for multiple testing in ANOVAs to preserve study power in supplementary dependent variable ANOVAs. Since we had independent predefined hypotheses associated with different well-known domains and CCPT-II variables, and since

Bonferroni-type testing (that all null hypotheses are true simultaneously) was of no interest, we report unadjusted p-values (Perneger, 1998). We assessed DSWPD vs controls post-hoc contrasts with Student's t-test (computationally identical to the LSD-test). Results were considered statistically significant when $p < 0.05$.

Five DSWPD patients had excessive omission errors in at least one evening test, most likely reflecting the clinically recognized severe lack of motivation or fatigue experienced by DSWPD individuals. These patients were otherwise typical and belong within the DSWPD spectrum. However, these extreme scores could also indicate a potential threat to performance validity (Sharland et al., 2018). To substantiate our main results, we therefore also provide separate cognitive domain estimates and background variables for the more typically performing DSWPD individuals (Appendix).

Results

Between-group questionnaires, DLMO, sleep diary and PSG-data are summarized in Table 1. As expected, DSWPD patients had a prolonged sleep onset latency, more of an evening chronotype, higher depression scores, a delayed DLMO, and delayed habitual sleep onset and offset. We observed no differences regarding total sleep time (TST) between the groups during habitual nights, while DSWPD patients as expected had significantly shorter TST during the forced (conventional) night.

DSPWD patients' mean baseline T-scores for nine of the ten available CCPT-II variables did not differ from controls. We observed good performance with low Hit RT STE in our control group with T-score 38.8 (SD 6.1) compared to patients T-score = 49.7 (SD 13.5); $p < 0.05$.

CCPT II primary variables

DSWPD patients had generally slower reaction times than controls, particularly for the morning tests (Table 2), and we found a significant Group-effect (Table 3 $p = 0.03$). Patients had greater variability in their reaction time (Hit RT STE) during the forced morning condition (Table 2) with a significant 3-way interaction (Table 3; $p = 0.01$). For omissions, we observed a significant time × group interaction (Table 3; $p = 0.03$), explained by DSWPD patients making more errors during the morning compared to controls, especially after the forced night (18.2 vs 0.9 omissions; post-hoc Student's t-test $p < 0.01$; Table 2).

When PSG-measured TST was controlled for, DSWPD patients still made more omission errors and had larger response variability shortly after early forced awakening (ANCOVA time × group interaction, F (1,33) = 4.6, $p = 0.04$, $\eta^2 = 0.12$ for omissions, and F (1, 33) = 7.7, $p = 0.009$, $\eta^2 = 0.19$ for Hit RT STE). For Hit RT, we only observed a non-significant trend, F (1, 33) = 2.8, $p = 0.10$, $\eta^2 = 0.08$. We observed no statistically significant difference for any of the primary variables for the habitual morning (all $p > .05$).

Factor-based cognitive domains

DSWPD patients had reduced focused attention after forced sleep (Figure 2, Table 2), with a significant 3-way interaction (Table 3; ANOVA, $p = 0.01$). There was also a significant between-group effect regarding focused attention (Table 3; $p = 0.02$), mainly driven by poor DSWPD patient performance with mean T-score = 69.2 during the early forced morning (Table 2). However, patients (Mean T-score = 51.2) performed generally worse than controls also in the habitual afternoon (mean T-score = 44.3; Student's post-hoc t-test $p < 0.05$, Table 2; Figure 1).

Sustained attention was mostly reduced at the habitual afternoon (T-score = 54.2 vs 46.7, post-hoc $p < 0.05$) as no change was observed after forced sleep (Table 2), despite a

statistically significant 3-way interaction (F = 7.5, p = 0.01; Table 3). We found no significant effects for impulsivity or vigilance (not tabulated).

When we controlled for PSG-measured TST, the significant differences remained for focused attention, with worse performance in DSWPD patients during the early forced awakening morning (ANCOVA time × group interaction, F (1, 33) = 4.5, $p = 0.042$, $\eta^2 = 0.12$). The opposite effect was observed regarding sustained attention during the habitual night, with DSWPD patients performing significantly better in the morning compared to controls (ANCOVA F (1,32) = 6.5, $p = 0.016$, $\eta^2 = 0.16$).

Subjective tiredness before the CCPT-II test

DSWPD patients reported more tiredness than controls after forced awakening (Table 1). A significant correlation within the patient group was found between habitual-morning tiredness and omissions (rho = 0.47, $p = 0.035$), and between forced-morning tiredness and focused attention (Figure 3; rho = 0.47, $p = 0.004$), omissions (rho = 0.57, $p = 0.009$), Hit-RT ($r = 0.46$, $p = 0.046$) and Hit-RT-variability ($r = 0.61$, $p = 0.004$).

Discussion

The main finding in this study was that DSWPD individuals had worse cognitive performance than controls upon awakening, and that this effect was more pronounced after forced early morning awakening than after awakening from habitual sleep. Upon awakening from a night with habitual sleep, DSWPD patients did not have individual worsening in cognitive performance. However, when compared to controls they had more omissions, and reaction times (RT) were longer and more variable shortly after habitual awakening. Cognitive performance worsened in DSWPD patients compared to healthy controls

immediately after forced early morning awakening, as patients' reaction time, variability and omissions were particularly increased. Moreover, by evaluating cognitive domain scores based on prior evidence of CCPT-II factor structure (Egeland, 2007, Egeland and Kovalik-Gran, 2010a), we noted that more tiredness reported by DSWPD patients was related to difficulties with focused attention.

Our results support that DSWPD individuals exhibit state dependent cognitive dysfunction likely linked to an excessive form of sleep inertia (SI) (Tassi and Muzet, 2000). Healthy individuals also experience SI yet the severity varies with stage upon awakening (Cavallero and Versace, 2003, Silva and Duffy, 2008) and duration of sleep (Dinges, 1990, Balkin and Badia, 1988). Symptoms are in general more severe upon awakening from a major sleep episode compared to awakening from a nap (Jewett et al., 1999, Achermann et al., 1995). The initial cognitive dysfunction dissipates over time, however, at a varying pace for different cognitive domains (Jewett et al., 1999, Marzano et al., 2011). The degree of SI is likely associated with chronotype, with evening-type individuals reporting greater SI upon early awakening (work days), but not during habitual sleep-wake schedule (weekends) (Roenneberg et al., 2003).

It is well known that SI impairs cognitive function in various tasks, including reaction/inhibition tests like the CCPT-II (Santhi et al., 2013, Burke et al., 2015, Tassi and Muzet, 2000, Solheim et al., 2014). A recent study by Ritchie et al. (Ritchie et al., 2017) shows that late chronotypes suffer longer lasting effects of SI (for cognitive throughput and speed) than early chronotypes, even when awakening at their habitual times. These results are similar to those we found in DSWPD patients in the present study, which may indicate that arousal processes operate at a slower pace for these individuals, causing longer lasting cognitive impairments upon awakening, regardless of sleep duration or timing. However, as we predicted, the effects of SI in DSWPD patients were considerably more pronounced

during early forced awakening. Although sleep duration may play a considerable role in SI (Roenneberg et al., 2003), our results show that DSWPD symptoms after the forced night schedule could not be explained by reduced TST.

SI-duration is also highly variable (minutes to hours) (Achermann et al., 1995, Jewett et al., 1999), and this factor can have clinical relevance in subjects with extreme SI-duration lengths. An SI duration paradigm was not included in the present study, but CCPT-II measures considering time-on-task effects (reflected in the sustained attention and vigilance domains) were rather stable in both patients and controls. Future studies should include a sleep restriction protocol for healthy subjects and phase-adjusted repeated CCPT-II testing to further investigate the influence of TST and actual neurobiological circadian phase.

Utilizing a novel approach in the context of DSWPD, we evaluated cognitive domain scores based on prior evidence of CCPT-II factor structure (Egeland, 2007, Egeland and Kovalik-Gran, 2010a). Prior work has suggested that operating with domains rather than single scores may improve the ability to differentiate between various psychiatric and neurological patient groups (Egeland and Kovalik-Gran, 2010b). Six of our twenty patients (30%) had forced-night T-scores for focused attention above 70, while few patients exceeded this value for the other variables. Hence, focused attention was the most sensitive measure, both on an individual- and group average level. In addition, worse focused attention within the DSWPD group was associated with higher subjective tiredness after forced awakening, thereby further supporting a link to SI symptoms.

Interestingly, sustained attention was rather low before (at baseline) the first habitual afternoon test, possibly reflecting a stress load or insufficient sleep time during the basal ambulatory night. However, sustained attention did not deteriorate in the habitual or forced mornings compared to the afternoon, suggesting that the significant 3-way interaction for

sustained attention may be a chance occurrence. No other domain exhibited any statistically significant results for DSWPD, in line with prior findings, suggesting that impulsivity and vigilance may be more useful in other disorders such as ADHD (Egeland, 2007).

Subtle indications of a cognitive trait dysfunction were also observed in DSWPD. Significant time × group interaction (with no three-way interaction; Table 3) and post-hoc patient-control differences for the habitual morning, i.e. reduced performance in DSWPD; were observed for focused attention (Figure 2) as well as for Hit RT, Hit RT STE and omissions (Table 2). This observation must be interpreted cautiously as patients went to bed and got up a somewhat earlier on the study morning than they reported in sleep diaries. However, sleep times seemed to be sufficient and within the normal range and sleep time was identical to diary-reported sleep times in Table 1. Of note, both early (Weitzman et al., 1981) and recent (Richardson et al., 2016) reports suggest that cognitive "insomnia-like" processes may contribute to the causation and maintenance of DSWPD. Chronic sleep deprivation due to mismatch of neurobiological circadian phase during habitual sleep times should also be considered, but seems less likely since sleep latency was increased among patients. Also depressive symptoms were probably less important, being an integral part of the DSWPD disorder and of borderline magnitude; between 'normal' and 'mild' (median BDI = 9). Accordingly, we believe that a real trait difference in cognitive function also is present in DSWPD. The large performance variability among DSWPD-patients, represented as very large SDs for several CCPT-II variables in Table 2, should also be emphasized. The large variability may to some degree be due to individual differences in circadian phase between patients.

We found that the patients with the most severe cognitive impairment at awakening also rated themselves as more tired. This finding may have clinical implications. Simple behavioral treatment procedures for the awakening phase could be developed. For the most severely affected patients, this may also include assistance to get up. Interesting results have been

found in a treatment trial where patients with DSWPD were randomized to either no treatment or to a combination of chronotherapy (morning bright light treatment and sleep phase advancement) and melatonin 3mg (Wilhelmsen-Langeland et al., 2013). Three months post treatment, the patients in the treatment group had a large and clinically significant phase advancement of the sleep period compared to the control group, but there were no corresponding improvement in CCPT-II measures (Wilhelmsen-Langeland et al., 2013, Saxvig et al., 2013). This could indicate that while the sleep-phase may normalize, cognitive function may not. The authors administered CCPT-II at fixed clock hours (e.g., 09:00, 11:00 and 13:00) in the latter study, not during SI, and the results are more appropriate for the possible cognitive trait-deficits in DSWPD. We propose to develop additional treatment modules to improve cognitive function during the awakening state, including perhaps brighter screen light and desks for standing during work hours.

The strengths of the present controlled study include a paired design with both habitual and forced night performance measured in the afternoon and shortly after awakening, a well-diagnosed patient sample and polysomnographic measurement of actual sleep time. One limitation is that eight patients had to be manually awakened at 12:00. For this reason, the first study night was not strictly habitual, but sleep length was adequate within normal range and even slightly longer for patients than for controls, so we believe that the effect from this limitation was minor.

Second, the laboratory environment might have contributed to earlier than usual bed times for both patients and controls during the habitual night. Lack of stimulation and dimmed light conditions might have caused the participants to go to bed earlier than under normal, everyday conditions.

Third, our participants were mainly university students. This might explain the rather mild delay in sleep phase compared to controls (about 2 hours). As university students, the patients may have learned to cope with their symptoms, nonetheless, they sought help as even this mild delay in sleep phase poses a problem for their future prospects and job opportunities.

In conclusion, we found that DSPWD was associated with both trait-like and state-dependent cognitive alterations. First, we confirmed that cognitive performance worsened in DSWPD-patients compared to healthy controls mainly after forced early morning awakening. Second, we found that the excessive SI reported by DSWPD patients was mainly reflected by a state-dependent reduced ability to focus attention. Third, upon awakening from a night with habitual sleep, patients had more omissions than controls, RT was longer, and RT-variability was increased, possibly suggesting a small cognitive trait dysfunction. Because brain regions associated with CCPT-II performance (Olsen et al., 2013) overlap with frontal brain regions that are also particularly prone to SI effects (Balkin et al., 2002, Trotti, 2017), we propose that future studies also should integrate online task performance with neuroimaging and/or neurophysiological techniques, in order to provide deeper insight into the problems of both SI in general (Trotti, 2017), and DSWPD in particular.

Appendix

We performed a supplementary analysis on the remaining 15 patients after removal of five with high omission counts. These 5 patients were otherwise typical, belong within the DSWPD spectrum, and they were kept in the main analysis. However, an excessive amount of omission errors could potentially indicate a threat to performance-validity, caused by factors unrelated to attention such as aggravation or lack of motivation (Sharland et al., 2018). Hit RT STE was also 30% higher in the low-omission sub-group (4.8 ms) compared to controls (3.5 ms; post-hoc Student's t $p = 0.02$) during forced early morning, although the 3-way interaction for Hit RT STE was just short of statistical significance (Supplementary Table 1, $p = 0.06$). A similar trend was observed for focused attention (Student's post-hoc t-test $p = 0.065$). The significant interaction for sustained attention ($p=0.01$) could not be confirmed by post-hoc statistics, however, because differences between patients and controls did not reach significance (Supplementary Table 1).

In addition, a significant forced-morning Hit RT STE remained among the 15 remaining patients (Supplementary Table 1), suggesting that even less affected individuals with more typical performance have increased SI-problems with some (probably transient) cognitive difficulties.

Supplementary Table 2 show that the high-omission subgroup generally were the ones with most excessive DSWPD-symptoms, i.e. the latest DLMO and light-off times, although significant only for 'eveningness'.

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Author Contribution:

BS collected the data, carried out a substantial part of the analyses and drafted the initial manuscript. AO contributed substantially with data analyses and revision of the manuscript. HK and KL contributed with assessment and inclusion of patients, and with revision of the manuscript. BB and MG contributed substantially with critical revision of the manuscript. TS revised the manuscript and supervised the writing process. All authors approved the final manuscript.

Conflict of Interest:

None.

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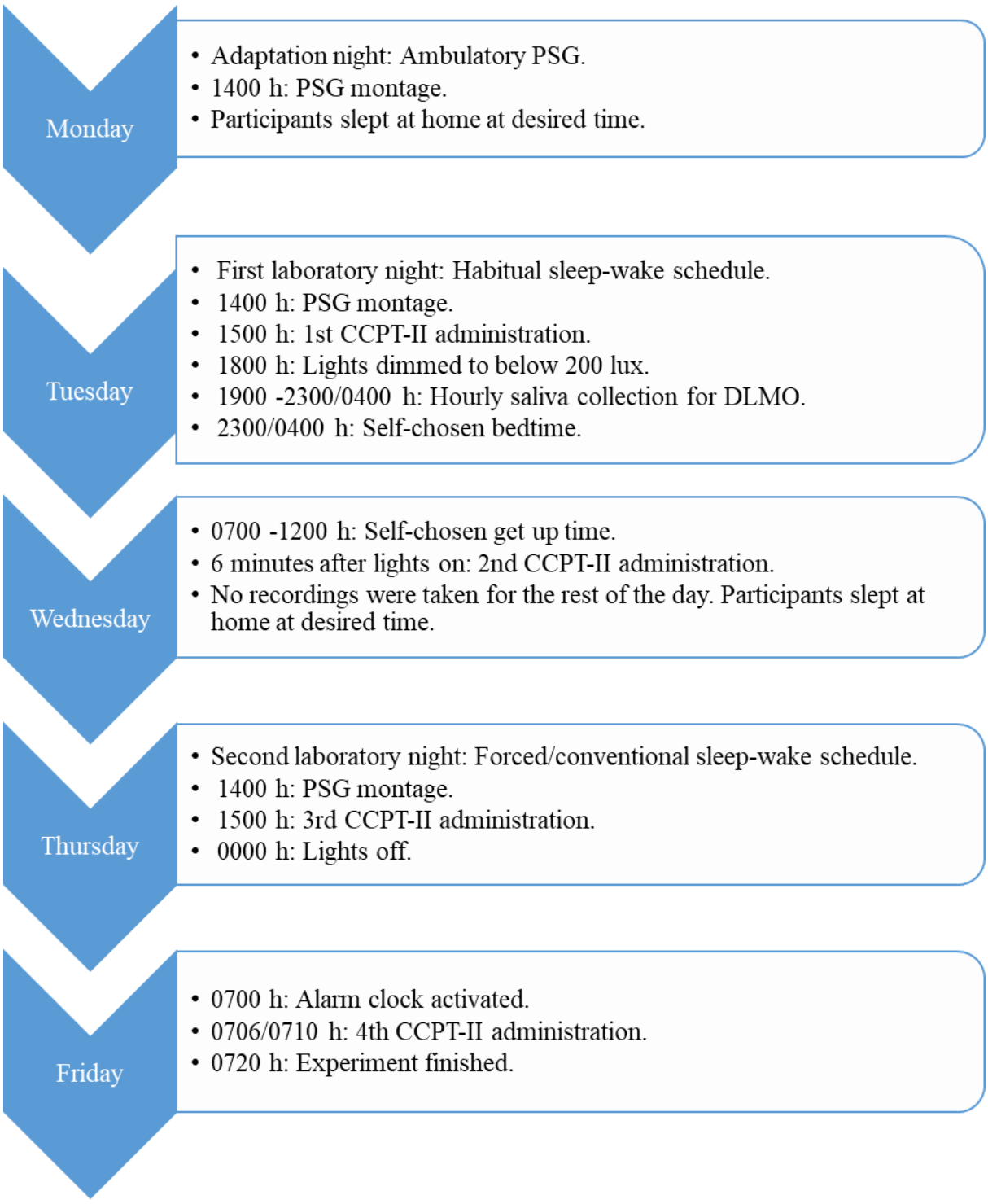
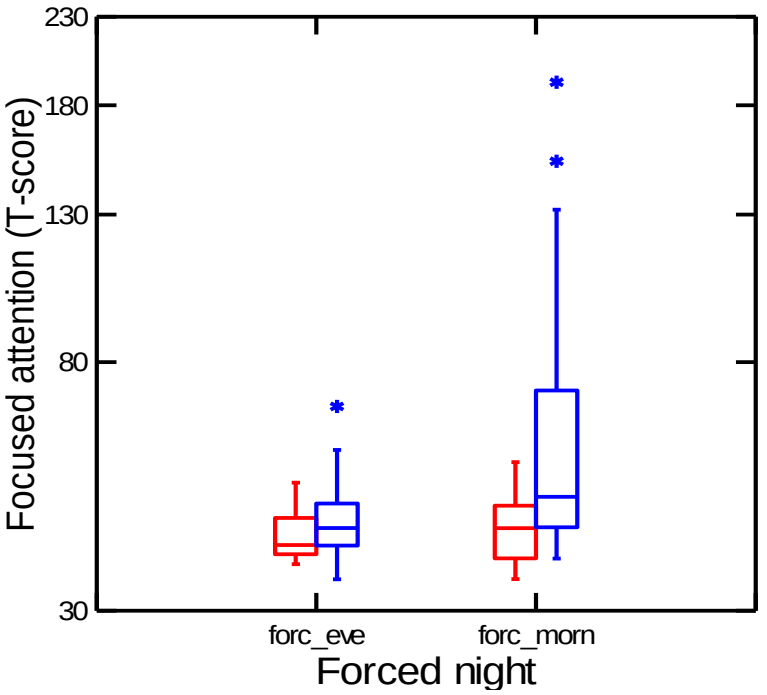


Figure 1. Overview of the experimental week.



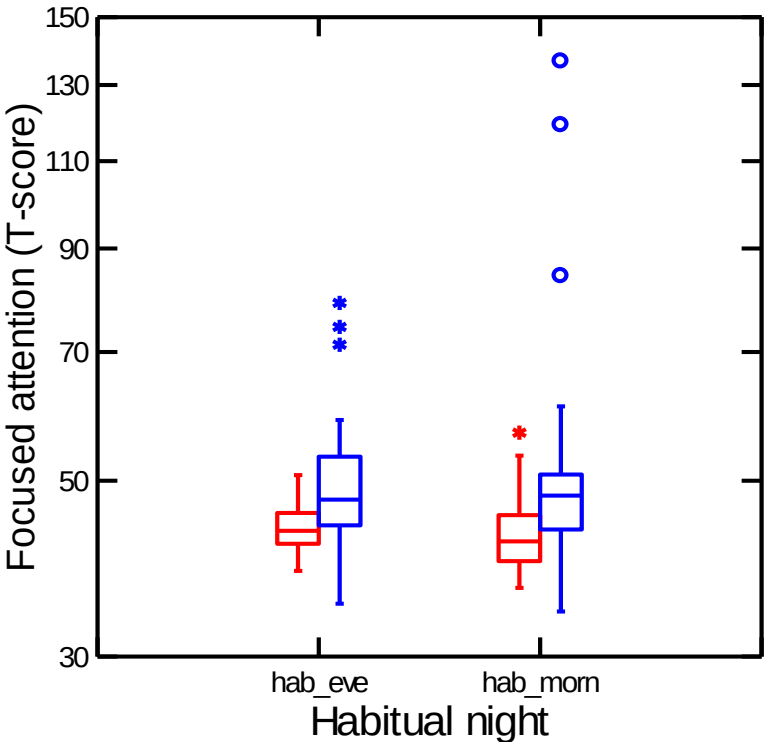


Figure 2. Box plot of the cognitive domain "Focused attention" in controls (red, left in pair, n = 16) and patients (blue, right in pair, n = 20). A significant worsening in the morning for patients is observed for the forced night. Patients performed worse also in the habitual evening. Median and interquartile range (IQR) defines box upper and lower borders (hinges). Whiskers display spread within hinge ± 1.5×IQR, stars fall within hinge ± 3×IQR, and circles are extreme outliers). Hab: Habitual night. Forc: Forced night. _eve: afternoon; morn: morning after awakening.

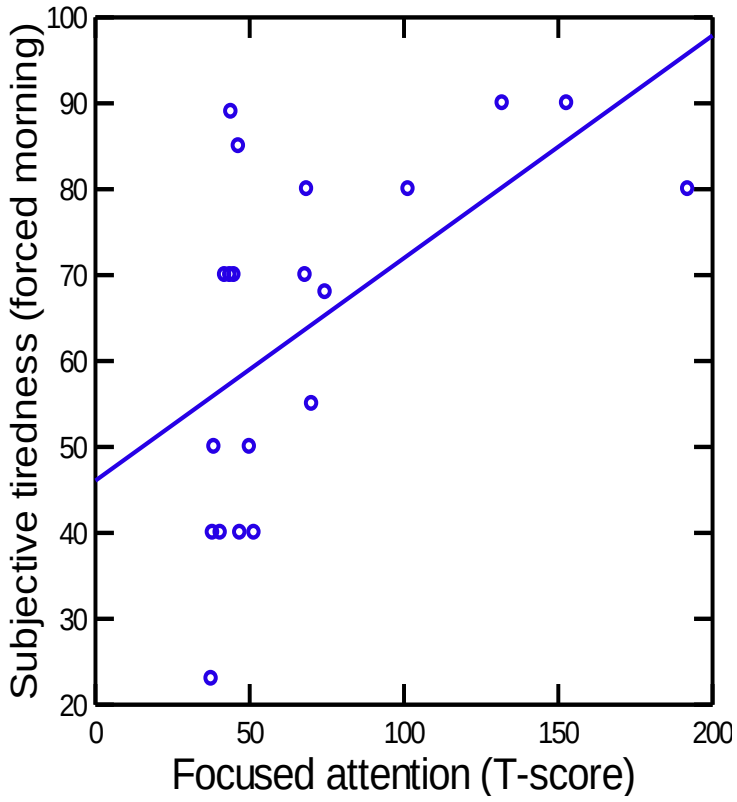


Figure 3. Significant correlation (Spearman rho = 0.47, p = 0.004) between tiredness and the cognitive domain “focused attention” measured in DSWPD patients shortly after early awakening at 07:00.

Table 1. Demographic, questionnaire, sleep-diary and polysomnographic data.

	DSWPD (n=20)	Controls (n=16)
Age (years)	24.8 (3.0)	24.4 (3.4)
Male/Female (no)	9;11	4;12
Student/Employed/Neither (no)	16;1;3	11;5;0
Early insomnia symptoms (0-4)[a]	2.9 (1.0)[f]	0.9 (0.7)
Morningness-Eveningness[b]	29.3 (4.9)[f]	54.7 (6.2)
Beck depression inventory	10.8 (9.4)[g]	3.4 (3.1)
DLMO[d] (h)	00:45 (01:24)[f]	22:22 (00:37)
Sleep diary		
Lights off (h)	02:38 (01:50)[f]	00:25 (01:10)
Lights on (h)	10:58 (01:50)[f]	08:51 (01:13)
PSG 1, habitual free sleep opportunity		
Lights off (h)	01:10 (01:18)[f]	23:29 (00:20)
Lights on (h)	10:53 (01:13)[f]	08:26 (00:50)
SOL to N1 (min) [e]	20.6 (8.8)	12.1 (6.6) [g]
TST (min)[c]	527.1 (101.8)	498.9 (52.4)
Tiredness score before CPT after habitual sleep (0-100)	46.5 (25.9)	38.9 (21.0)
PSG 2, conventional forced sleep schedule		
SOL to N1 (min)	47.9 (35.7)[f]	11.5 (5.8)
TST (min)[c]	334.9 (62.5)[f]	395.8 (7.5)
Tiredness score before CPT after forced sleep (0-100)	64.0 (20.3)[h]	48.1 (21.3)

Mean value (SD in parentheses) or count (no) is tabulated. h: hours, [a] Scores for sleep onset problems last 3 months (scored as 0=never to 4= daily in the Karolinska sleep questionnaire). [b],Horne-Ostberg questionnaire, [c]TST: total sleep time. [d] Dim light melatonin onset (4 pg/ml threshold). [e] SOL: sleep onset latency. [f] $p<0.0005$, [g] $p<0.01$, [h] $p<0.05$ (Descriptive Mann-Whitney U test).

Table 2. Reaction time, omissions and cognitive attention-domain variables from Connors continuous performance test (CCPT-II).

	DSWPD (n=20)		Controls (n=16)	
	Afternoon	Morning	Afternoon	Morning
Habitual sleep schedule				
Hit RT (ms)	352 (42)	**363 (84)[e]**	331 (32)	322 (31)
Hit RT-STE (ms)	**5.6 (2.6)[f]**	**6.3 (5.3)[e]**	3.8 (0.7)	3.5 (0.5)
Omissions	4.1 (8.9)	**8.4 (20.7)[e]**	0.9 (1.0)	0.6 (1.2)
Focused attention[a] (T)	**51.2 (11.5)[e]**	56.1 (26.8)[(e)]	44.3 (3.3)	43.4 (5.4)
Sustained attention[b] (T)	**54.2 (14.4)[e]**	49.6 (5.7)	46.7 (5.0)	51.2 (4.6)
Forced sleep schedule				
Hit RT (ms)	330 (44)	**377 (114)[e]**	307 (22)	313 (29)
Hit RT STE (ms)	4.1 (2.0)	**8.5 (9.0)[f]**	3.3 (0.7)	3.5 (0.9)
Omissions	1.1 (2.5)	**18.2 (37.4)[f]**	0.6 (0.9)	0.9 (1.7)
Focused attention[a] (T)	44.8 (8.0)	**69.2 (43.0)[f]**	41.9 (4.8)	43.1 (6.3)
Sustained attention[b] (T)	50.8 (6.9)	53.2 (8.6)	51.2 (4.2)	49.6 (5.9)

Mean and SD in parentheses. Hit RT: reaction time. STE: Standard error. T: T-score (high values represent worse performance).

Cognitive domain variables: [a]average of variability, Hit RT STE, perseverations and omissions, [b]average of Hit RT Block Change and Hit SE block change.

Student´s post-hoc t-test (DSWPD vs Controls): [e]$p<0.05$, [(e)] $p<0.07$, [f]$p< 0.01$

Table 3. Statistical differences between DSWPD and controls regarding the change in cognitive performance from afternoon to morning and the difference in performance between the forced and the habitual morning.

	Group	Condition × Group	Time × Group	Condition × Time × Group
HIT RT	**5.3 (0.03)**	1.0 (0.32)	3.3 (0.08)	1.4 (0.25)
Hit RT STE	**9.2 (0.005)**	0.1 (0.73)	**4.8 (0.03)**	**6.7 (0.01)**
Omissions	**5.6 (0.02)**	0.0 (0.90)	**5.2 (0.03)**	1.5 (0.23)
Focused attention	**6.1 (0.02)**	1.3 (0.26)	3.9 (0.06)	**6.6 (0.01)**
Sustained attention	2.2(0.15)	0.3 (0.61)	1.2 (0.29)	**7.5 (0.01)**

Repeated measures ANOVA F-statistic (df 1,34) and p-value in parentheses. Dependent variables were LN-transformed before analysis. Time: Evening-morning difference. Condition: Forced awakening - habitual sleep difference. Group: DSWPD-control group difference. P-values below 0.05 in bold. F-values for non-group factors are not shown. STE: Standard error.

Supplementary Table 1. Mean values (SD) for primary and domain CPT-II measures for the low-omission subgroup (n=15).

	Habitual afternoon	Habitual morning	Forced afternoon	Forced morning
Primary CCPT-II variables				
Hit RT (ms)	341 (35)	333 (37)	324 (42)	333 (37)
Hit RT STE (ms)[c]	5.1 (2.5)	4.5 (2.5)	3.8 (1.8)	**4.8 (1.7)[a]**
Omissions	1.5 (2.4)	1.3 (1.9)	0.5 (0.8)	1.8 (2.3)
T-scores for CCPT-II-based domain variables				
Focused attention	48.5 (10.1)	47.0 (11.5)	43.5 (6.4)	50.4 (13.1)[b]
Sustained attention[d]	51.8 (10.9)	49.3 (4.8)	48.9 (5.8)	52.3 (8.2)

Mean (SD) is tabulated. Hit RT: reaction time. STE: Standard error.

ANOVA results: [c]Group effect F=4.5 (p=0.04) and Condition × Time × Group effect F=3.7, p=0.06. [d]Group effect F=0.5 (p=0.48) and Condition × Time × Group effect F=6.9, p=0.01

Post-hoc Student's t-test: [a]p=0.02, [b]p=0.065 (patient subgroup vs control group). Control group mean and SD is shown in Table 2.

Supplementary Table 2. Descriptive, clinical and PSG-data for DSWPD patients with low and high omission scores on CCPT-II (mean and SD).

	Low omission subgroup (n=15)	**High omission subgroup (n=5)**
Age	25.5 (3.0)	22.8 (2.2)
Male/Female (no)	8;7	1;4
Morningness-Eveningness	30.7 (4.6)	25.0 (3.4) [1]
Beck depression inventory	10.7 (10.1)	11.2 (8.0)
DLMO[2] (h)	00:32 (01:27)	01:24 (01:08)
Sleep diary		
Lights off (h)	02:41 (01:43)	03:10 (02:15)
Lights on (h)	11:12 (01:52)	11:09 (01:22)
PSG 1, free sleep opportunity		
Lights off (h)	00:51 (01:17)	02:08 (00:53)
Lights on (h)	10:59 (01:04)	10:36 (01:42)
TST (min)	562.2 (88.6)	454.3 (120.4)

[1] $p<0.05$ (Descriptive Mann-Whitney U test). [2] Dim light melatonin onset (4 pg/ml threshold). h: hours, SOL: sleep onset latency. TST: total sleep time.