Title: Patients with Delayed sleep-wake Phase Disorder show Poorer Executive Functions compared to Good sleepers

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Abstract

Objective: Delayed Sleep-Wake Phase Disorder (DSWPD) is associated with negative outcomes including reduced daytime performance and difficulties with treatment adherence. These outcomes are mediated by executive functions (EF). In this study, we investigated whether patients with DSWPD report inferior EF compared to a control group. The study consisted of 40 patients diagnosed with DSWPD (12 males, mean age 20.7 (± 3.1)) and 20 healthy controls (6 males, 21.3 (± 2.2), p=1.00) between 16 and 25 years (p= .42).

Methods: Behavior Rating Inventory of Executive Function - Adult version Self-Report (BRIEF-A) was used for adults ≥18 years (DSWPD n=28; controls n=17) whereas Behavior Rating Inventory of Executive Function Self-Report Version (BRIEF-SR) was used for assessment of EF in adolescents <18 years (DSWPD n=12; controls n=3). Independent samples t-tests were used to compare patients to controls.

Results: The total group of patients with DSWPD scored significantly poorer compared to the control group on the main indexes; Behavioral Regulation Index (BRI) (p = <.0005), Metacognition Index (MI) (p = <.0005), and Global Executive Composite (GEC) (p = <.0005). The adult group with DSWPD scored significantly poorer than the adult control group on eleven of the twelve BRIEF-A scales. Among patients <18 years, the DSWPD-group scored significantly poorer than the control group on eight of the thirteen BRIEF-SR-scales.

Conclusion: Patients with DSWPD reported significantly poorer EF compared to controls. Assessment of EF in patients with DSWPD can be valuable for understanding the consequences of the disorder and regarding treatment tailoring and adherence.

Key words: Delayed sleep-wake phase disorder, executive functions, BRIEF-SR, BRIEF-A, attention deficits

Delayed Sleep-Wake Phase Disorder (DSWPD) is a circadian rhythm sleep-wake disorder characterized by `a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of inability to fall asleep and difficulty awakening at a desired or required clock time` (p. 191) [1]. According to diagnostic criteria, the symptoms must be present for at least three months, and data based on one-week sleep diary or actigraphy recording (including both school/workdays and days off) must be provided to confirm the diagnosis [1].

According to the American Academy of Sleep Medicine, DSWPD is most common among adolescents and young adults, with a reported prevalence in an adolescent population ranging from 7% to 16% [1]. The prevalence, however, seems to vary significantly according to the assessments and operationalisations used [2]. During puberty, a biologically based delay in the sleep phase occurs together with a slowing of the accumulated homeostatic sleep pressure [3-6], which predisposes young individuals towards a delayed sleep pattern and to develop DSWPD. The aetiology of DSWPD is yet unclear, but different paths to the development and/or maintenance of the disorder have been proposed. These include physiological, genetic, behavioural and psychological factors [2].

At odds with the delayed sleep pattern, individuals with DSWPD are often required to rise early in the morning due to societal demands such as school or work. Consequently, sleep duration is often restricted for patients with DSWPD. This is reflected in studies reporting that these patients on average have a shorter total sleep time, compared to controls [7, 8]. They also typically complain about excessive daytime sleepiness [9, 10], which is related to distress and impaired function [11]. However, when individuals with DSWPD have the opportunity to sleep

ad libitum, sleep duration and sleep quality seem to be similar to that of age- matched controls [6].

Daytime sleepiness and chronic sleep loss can have a negative impact on cognitive functioning. Studies have indicated that sleep deprivation and later sleep rhythm both are linked to impaired cognitive performance, including poorer executive function (EF) and working memory. One study, including a 14 minute continuous performance test reflecting different aspects of attention (Conners` Continuous Performance Test (CPT)) [15], found that patients with DSWPD showed impaired function compared to controls, and that the effect was larger when the patients were assessed in the morning [16], which co-occur with the time when patients with DSWPD most likely are at their circadian low. Previous research has further reported that adolescents with excessive sleepiness show significantly poorer performance on tests of EF compared to adolescents who report less sleepiness [17]. Not all patients with DSWPD are necessarily excessively sleepy if they are able to sleep at their own circadian preference, however, DSWPD-patients have previously been shown to score much higher on the Epworth Sleepiness Scale [18] compared to controls (10.3±0.6 for patients compared to 5.2±0.8 for controls, $p = <.00005$) [10]. To our knowledge, no studies have addressed the relationship between DSWPD and self-reported problems related to EF.

Reduced EF is a core symptom experienced by patients with Attention Deficit Hyperactivity Disorder (ADHD) [19], and the overlap between sleep problems and symptoms of ADHD are shown in several studies [20-22]. The cognitive dysfunction associated with both DSWPD and ADHD may suggest that behaviours associated with DSWPD, such as inattention or lack of concentration, can sometimes be erroneously identified as symptoms of ADHD, and vice versa [23]. Also, much like for patients with DSWPD, patients with ADHD also exhibit delays in

their circadian timing that might contribute to EF deficits [24]. In a treatment study, nearly half of the included subjects with DSWPD (aged 10 to 18) had comorbid ADHD [25]. Melatonin treatment synchronized their sleep-wake rhythm to a more desirable pattern and further contributed to a reduced need for psychotherapy and/or stimulant medication.

More studies are thus called for to investigate EF among patients with DSWPD, firstly; to inform clinicians towards a better accuracy in differential diagnostics, and secondly; to improve clinicians' ability to tailor the treatment to the patients' needs. On that account, the purpose of the present study was to investigate if patients with DSWPD show significant deficits in self-reported EF compared to a control group without sleep difficulties. We hypothesized that patients with DSWPD would show poorer self-reported EF than the control group.

Method

Participants

Initially, 264 individuals made contact to be considered for inclusion in the DSWPD-group and likewise 55 individuals for the control group (see Figure 1). The final study group consisted of 40 patients diagnosed with DSWPD (28 females) and 21 healthy controls (15 females). However, due to an administrative error one control subject did not complete the required instruments and was therefore excluded. The mean age of the 60 included participants with valid data was 20.7 (± 3.1) years in the patient group, and 21.3 (± 2.2) years in the control group, p= .42 (two-tailed). The two groups did not significantly differ on IQ-score or on school grade average (Raven, 2000; Wilhelmsen-Langeland, Saxvig, Pallesen, Nordhus, Vedaa, Sørensen, et al., 2013). The two groups neither differed on total sleep time nor percentage spent in each sleep stage as measured by polysomnographic recordings (when they slept according to their own preferred timing), nor in terms of sleep duration measured by the self-report

questionnaire Pittsburgh Sleep Quality Index (PSQI) [6, 10, 26]. All participants in the present study were enrolled in high-school, college or university, except one who was employed. The proportion of participants within the different educational categories did not significantly differ between the two groups (p=0.15). For more detailed information about the study samples, please confer previous publications [6, 10].

Participants included in the present study were adolescents and young adults between 16 and 25 years of age with symptoms confirming the diagnostic criteria of DSWPD (at the time of recruitment named delayed sleep phase syndrome) according to the second edition of the International Classification of Sleep Disorders [27], and healthy controls. All participants were recruited through advertisements at high schools, a college and a university (i.e. e-mails, flyers, posters and stands). The participants with DSWPD also took part in a randomized controlled trial (RCT) (ClinicalTrials.gov identifier: NCT00834886) investigating the effects of bright light therapy and exogenous melatonin. The study reported here is, hence, part of a larger study protocol [6, 10, 28-30].

The inclusion requirements for the study were; 1) participants in the DSWPD group had to fall asleep later than 2 a.m. ≥ 3 days per week, show a delayed sleep pattern with long sleep latencies, late wake-up times and/or short sleep duration as confirmed by 1 week of sleep diary whereas 2) the participants in the control group had to consider themselves as good sleepers with a normal circadian rhythm and were required to report falling asleep before midnight at least 3 nights a week, not fall asleep after 2 a.m. more than twice a week and report sleep latency of >30 minutes less than three nights per week and exhibit normal wake-up times for their age, also confirmed by one week of sleep diary. Exclusion criteria were somatic disorders (e.g. diabetes,

rheumatoid arthritis, other sleep disorders or conditions assumed to affect sleep (e.g. sleep apnoea (all participants went through a polysomnographic screening (PSG)), migraine, B12 deficiency), and psychological disorders of moderate to severe level (screened for in the initial telephone-interview where participants were asked whether they had other illnesses or symptoms and later in the protocol, with the Structured Clinical Interview for DSM-IV, Axis I diagnoses (SCID-I interview)) [31], an IQ-score below 70 (equivalent to intellectual disability according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [32]) on a test of intellectual function (IQ) [33], use of sedative psychoactive drugs or medications (e.g. anti-histamines, antidepressants or hypnotics) during the past 4 weeks, breastfeeding or pregnancy (all female participants took a pregnancy test) and night work. None of the participants had at any time previously been diagnosed with or received treatment for DSWPD and none had comorbid psychiatric diagnoses on inclusion in the study (such as confirmed ADHD/ADD).

(Insert Figure 1 around here)

Ethics

Informed consent was obtained following full explanation of the study protocol. For participants under 18 years of age, parents were required to sign the consent form before inclusion and to give consent verbally. A compensation fee (approximately 25 EUROS) was given to all participants for time invested. The Regional Committee for Medical, Health Research Ethics in Western Norway (REK Vest; project number 2009/506, 012.08), the Norwegian Social Data Service (reference number 18261/2/LT) and the Norwegian Medicines Agency (reference number 08/3340-4) approved the study.

Instruments

Behaviour Rating Inventory of Executive Function Self-Report (BRIEF-SR) version was used for assessment of EF in adolescents aged 16-17 years [34], whereas the BRIEF Adult version, self-report (BRIEF-A) was used to assess EF in adults aged 18-25 years.

The BRIEF-SR consists of eight subscales and provides two broader indexes and one composite score. The broad index Behavioural regulation index (BRI) includes the subscales "Inhibit", which refers to control of impulses and behaviour, and the ability to appropriately stop and modulate or regulate own behaviour at the proper time or in the proper context; "Shift", which refers to the ability to move freely from one situation, activity or aspect of a problem to another as the situation demands (captured by the sub-scale "Behaviour shift") and make transitions and solve problems flexibly (captured by the sub-scale "Cognitive shift"); "Emotional control" which refers to the ability to modulate or regulate emotional responses appropriately to situational demands or contexts and "Monitor" which refers to the ability to be aware of strengths and weaknesses and be aware of own behaviour and its impact on others. The broad index Metacognition index (MI) consists of the subscales "Working memory", which refers to the ability to hold information in mind for the purpose of completing a task or making the appropriate response; "Task completion", involving the ability to complete schoolwork or chores in a timely fashion and finish tests within the time limit, working at a satisfactory pace; "Plan/organize", referring to the ability to anticipate future events or consequences, use goals or instructions to guide behaviour in context, develop or implement appropriate steps ahead of time to carry out an associated task or action; and "Organization of materials", referring to the ability to keep work and school materials organized and the ability to organize the environment such as

backpack and bedroom [34]. The combined BRI and MI score gives an overall composite index denoted Global executive composite (GEC) score. In the present study, 3 participants from the control group and 12 participants with DSWPD completed the BRIEF-SR.

The BRIEF-A consists of nine subscales and provides the same two broader indexes BRI and MI and the overall GEC as the BRIEF-SR. The BRI includes the same subscales (Inhibit, Shift (without the sub-entities "Behavioural- "and "Cognitive shift"), Self-monitor and Emotional control) as described above. The index MI on BRIEF-A includes the same subscales as on the BRIEF-SR (Plan/organize, Working memory, Organisation of materials) but includes "Task monitor" (instead of "Task completion"), which refers more to the awareness of own behaviour and impact on others and "Initiate" referring to the ability to begin an activity and to independently generate ideas or problem-solving strategies. In the present study, 17 participants from the control group and 28 participants with DSWPD completed the BRIEF-A.

The scoring program for the BRIEF provides a protocol summary report, which gives age-specific norms, with results expressed as T-scores. A T-score of 50 represents the mean of the T-score distribution and a T-score of 65 represents 1.5 standard deviations above the mean, which is the threshold for a clinically elevated score. The higher the T-score, the poorer the EF [34]. The BRIEF-SR and BRIEF-A were administered at the first meeting with each participant. This meeting was arranged between the researchers and the participant preferably within working hours (8 am to 4 pm), or in the evening if more convenient for the participant. The BRIEF-SR and BRIEF-A were never completed early in the morning. Since the BRIEF-SR and BRIEF-A are standardized self-report measures that assess a person's general view of her/his own EF [34], time-of-day should have minimal impact on the results. Cronbach`s alpha for the normative sample was moderate to high, ranging from .72 to .96 [34]. Cronbach`s alpha for BRIEF-SR in

the present study ranged from .87 to .92. For the BRIEF-A, Cronbach`s alpha ranged from .83 to .89.

Statistical Analysis

IBM® SPSS® Statistics Version (23.0) for (Mac®) (IBM Corporation, Arnink, NY) was used for the statistical analyses. The age difference among the participants meant they had to complete two different versions of the BRIEF. We thus performed a Chi-square test for independence (with Yates Continuity Correction), which indicated no significant association between groups (control vs. DSWPD) and BRIEF versions (BRIEF-SR vs. BRIEF-A), $\chi 2$ (df =1, n=60) = .90, p=.34, phi = .16. Independent samples *t*-tests were performed on all BRIEF subscales and composite scores to test for differences between the DSWPD-group and the controls. Differences were considered significant when *p*-values were < .05. Effect sizes are provided in Tables 1, 2 and 3 as Cohen's *d (Cohen's d = M1 - M2 / spooled, where spooled =√[(s 12+ s 22) / 2]rYl = d / √(d2 + 4)* (http://www.uccs.edu/~lbecker/). As a benchmark for interpreting effect sizes (Cohens d), 0.2 is regarded as a small effect, 0.5 as a medium effect and 0.8 as a large effect [35].

Results

The patients with DSWPD scored significantly poorer compared to the control group on the main clinical indexes BRI, MI, and GEC. Results from BRIEF-SR and BRIEF-A were combined for these analyses and in Table 1. Effect sizes were large (Table 1).

(Insert Table 1 around here)

BRIEF-SR

Among subjects <18 years, the patients with DSWPD scored significantly poorer than the control group on the BRIEF-SR's composite scores BRI, MI and GEC. The patients with DSWPD reported more severe problems than the control group on several subscales: Inhibit, Cognitive shift, Monitor, Plan/organize and Organization of materials. Effect sizes were large (Table 2). There were no significant differences between the groups in terms of overall shifting (Cognitive and Behavioural combined), Behavioural shifting, Emotional control, Working memory and Task completion.

(Insert Table 2 around here)

BRIEF-A

The adult patients with DSWPD scored significantly poorer on all the composite scores (BRI, MI and GEC). They scored significantly poorer on the subscales Inhibit, Shift, Emotional control, Initiate, Plan/organize, Working memory, Organization of materials and Task monitor compared to the adult control group. Effect sizes were large (Table 3). Reports on the Self-monitor BRIEF-A subscale were not significantly different between the two groups.

(Insert Table 3 around here)

Discussion

In this study we investigated whether patients with DSWPD show deficits on self-reported measures of EF compared to controls. Our findings show that patients with DSWPD obtained higher scores on all the BRIEF-SR/-A indexes (BRI, MI and GEC) than controls. These

indexes reflect different types of behaviour related to different domains of EF. BRI reflects self-regulation in terms of cognition, emotions and behaviour, as well as flexibility in shifting between problem solving sets [34]. The subscales that compose BRI are also of importance for problem solving and self-regulation. MI relates to the ability to perform future-oriented problem solving and planning, as well as the ability to sustain task completion efforts in working memory. These are important features of attention, and are key factors influencing everyday function as well as academic performance. Working memory is crucial for carrying out multistep activities and following instructions. If basic abilities linked to working memory capacity are impaired, use of metacognitive knowledge and the ability to strategically control memory functions will also be impaired [34]. It is conceivable that the impaired attention and working memory associated with DSWPD mediates reduced school performance and problems regarding adherence to treatment regimens found among these patients. The findings in the study may also shed a wider light on the described psychosocial conflicts experienced by patients suffering from DSWPD, such as keeping appointments with family and friends and being able to pay attention in class [29]. Reduced EF in these patients can thus be a consequence of chronic sleep restriction, their delayed circadian rhythm [6], or both. The latter is in line with findings by Kuula et al. (2018), showing that delayed sleep phase is associated with poorer EF in a non-clinical sample. The patients with DSWPD are also repeatedly required to function (at school/work) at times when their own circadian rhythm promotes sleep (early in the morning).

Executive Functions, Comorbidity and Attention Deficits

It has been suggested that sleep disorders that lead to excessive daytime sleepiness, such as DSWPD, and the concomitant behavioural and cognitive consequences, could emerge as behaviour characteristic of patients with ADHD [36]. This notion is supported by findings

showing that patients with ADHD are also reported to be more vulnerable to DSWPD [34]. Loss of sleep and ADHD have both been associated with impaired EF. ADHD symptoms can also be aggravated by sleep loss [25]. The risk of misdiagnosing DSWPD as ADHD and vice versa is thus presumably high and may potentially lead to erroneous treatment [25].

According to our findings, there was a clear association between DSWPD and impaired EF. However, no conclusions regarding the causal relationship between DSWPD and EF can be drawn from the present study, and it is possible that there is a bidirectional relationship between EF and a delayed sleep phase, where poor EF can contribute to later bedtime, and loss of sleep can lead to poorer EF. A recent study on a non-clinical sample concluded that proneness to eveningness or later circadian rhythm was related to worse trait-like behavioural regulation characteristics, while shorter sleep duration was more related to worse immediate performance (state-like) [14]. This possible bidirectionality could be investigated by administering BRIEF before and after treatment for DSWPD. If treating DSWPD improves EF, the circadian rhythm disorder may precede the development of EF deficits. On the other hand, if EF remains unchanged following treatment, then the EF deficit likely precedes the development of the disorder. To our knowledge, this issue has not yet been explored.

In a previous study focusing on personality of subjects with DSWPD, we found that the DSWPD group had a different profile than the control group. Specifically, the former group scored much lower on the personality trait Conscientiousness [10]. This personality trait relates to self-discipline, order, dutifulness, competence, achievement striving and deliberation [37]. This finding was also corroborated by a study including a DSWPD sample from Australia [38]. The personality trait Conscientiousness shares characteristics with EF, and the discussion about

bidirectionality and preceding factors may be relevant for personality traits as well as for EF in DSWPD.

Strengths and Limitations of the Study

The use of BRIEF to measure different aspects of EF has shown good validity in previous studies. In a recent study on EF in patients with substance abuse disorder, BRIEF was described as the most sensitive measure of EF compared to the Stroop test, Trail Making Test and the Iowa Gambling Task [39]. Furthermore, BRIEF has demonstrated convergent validity with other measures of inattention, impulsivity, and learning [40]. Others have argued that self-report scales in general have a higher ecological validity as opposed to data collected in more artificial laboratory settings, such as performance tests set up to test immediate performance in a laboratory [41].

Patients with DSWPD in the present study had similar scores as the control group on IQ-measures and self-reported school grades although many previous studies show associations between DSWPD and poorer academic performance [7, 42, 43]. The fact that the patients with DSWPD in this study nevertheless scored much poorer that the control group and that the effect sizes were so large, suggests that the findings are of high significance to the understanding and treatment of patients with DSWPD. The patients with DSWPD included in the present study can be considered as a high functioning group relative to the average DSWPD-patient who does not join studies with extensive research protocols. Their high level of functioning may in part be explained by the recruitment procedures, seeking participants from upper secondary school and university. It is likely that this group possesses abilities that to some extent help them compensate for the reduced executive capacity that may derive from their sleep status. However, the control group was recruited using the same procedures, hence it is reasonable to interpret the reported

group differences as a reflection of differences in sleep between the groups and not as a reflection of sampling differences. In clinical settings, one is more likely to meet DSWPD-patients who have dropped out of school or are unemployed because of their sleep-wake difficulties and the co-occurring psychosocial problems that may follow. Such young adults with DSWPD often experience different and even more severe challenges related to EF than the participants in the present study [23]. Hence, to include patients from a clinical in-patient group instead of from high-school/university, might have given us more valid data to such populations. The overall study sample size was small, and a larger sample would probably provide more reliable data. Also, the sub-sample in the analyses for the BRIEF-SR is unfortunately very small with very few participants in the control group (n=3) versus the patient-group (n=12). The results on BRIEF-SR should therefore be interpreted with caution. The groups are, however, defined by age (those under 18 were given the BRIEF-SR), hence overall, we regard the lack of statistical power as more of a limitation than i.e. added heterogeneity to this sub-sample.

Implications for Future Research

Due to their sleep disturbances, patients with DSWPD may be more cognitively impaired in school and work settings than their cognitive potential should imply. It therefore seems important to assess sleep-patterns before diagnosing or testing cognitive functions. Furthermore, it would be of interest to investigate how treatment can influence DSWPD-patients' EF. More specifically, one could examine whether adolescents with attention deficits that meet the criteria for DSWPD will improve on EF following effective treatment of their sleep-wake phase problems.

Given that sleep loss deteriorates EF, the importance of early intervention and treatment is significant. We thus suggest that future studies address the directionality of the relationship between DSWPD and EF and investigate how different EF-components specifically are influenced by sleep problems and sleep loss.

Conclusion

Patients with DSWPD scored significantly poorer compared to controls on several indicators of EF measured by BRIEF. Assessment of EF in patients with DSWPD can be of significant value in terms of differential diagnosis, treatment tailoring and adherence to treatment, as well as for understanding the everyday consequences of DSWPD.

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