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ADHD, circadian rhythms and seasonality

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ABSTRACT

Objective: We evaluated whether the association between Adult Attention-Deficit/Hyperactivity Disorder (ADHD) and Seasonal Affective Disorder (SAD) was mediated by the circadian rhythm.
Method: Data of 2239 persons from the Netherlands Study of Depression and Anxiety (NESDA) were used. Two groups were compared: with clinically significant ADHD symptoms (N = 175) and with No ADHD symptoms (N = 2064). Sleep parameters were sleep-onset and offset times, mid sleep and sleep duration from the Munich Chronotype Questionnaire. We identified the prevalence of probable SAD and subsyndromal SAD using the Seasonal Pattern Assessment Questionnaire (SPAQ). Clinically significant ADHD symptoms were identified by using a *T* score>65 on the Conners Adult ADHD Rating Scale.
Results: The prevalence of probable SAD was estimated at 9.9% in the ADHD group (vs. 3.3% in the No ADHD group) and of probable s-SAD at 12.5% in the ADHD group (vs 4.6% in the No ADHD group). Regression analyses showed consistently significant associations between ADHD symptoms and probable SAD, even after adjustment for current depression and anxiety, age, sex, education, use of antidepressants and benzodiazepines ($B = 1.81$, $p < 0.001$). Late self-reported sleep onset was an important mediator in the significant relationship between ADHD symptoms and probable SAD, even after correction for confounders (total model effects: $B = 0.14$, $p \leq 0.001$).
Conclusion: Both seasonal and circadian rhythm disturbances are significantly associated with ADHD symptoms. Delayed sleep onset time in ADHD may explain the increase in SAD symptoms. Treating patients with SAD for possible ADHD and delayed sleep onset time may reduce symptom severity in these complex patients.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that commences in childhood, and often persists throughout the lifespan (Simon et al., 2009). The estimated prevalence of ADHD is 3.4% in adults (Fayyad et al., 2007). The clinical presentation of ADHD in adults is marked by inattentiveness and impulsivity, with fewer hyperactivity symptoms than in childhood. Adult hyperactivity may be internalized as inner restlessness (Biederman et al., 2000). Adult inattention is characterized by difficulty in planning and organizing tasks, poor listening skills, distraction and procrastination (Turgay et al., 2012). Impulsivity may result in interrupting others, poor self-control, reckless driving and impatience (Turgay et al., 2012).

In addition, adult ADHD is comorbid with mood, anxiety and sleep disorders, amongst others (Fayyad et al., 2007; Lin et al., 2016; Vingilis et al., 2015). Seasonal Affective Disorder (SAD) is a type of recurring major depression with a seasonal pattern. It frequently co-occurs with adult ADHD, with a prevalence of up to 27%, as compared to 6% in the general population (Amons et al., 2006; Levitan et al., 1999; Rosen et al., 1990). SAD is characterized by major depressive episodes during autumn and/or winter, which

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remit in spring (American Psychiatric Association, 2013; Rosenthal et al., 1984). Symptoms include difficulty concentrating, anhedonia, fatigue, forgetfulness, as well as the co-called atypical depressive symptoms: sleep disturbance (tendency to sleep longer), hyperphagia and weight increase (American Psychiatric Association, 2013).

ADHD is also associated with circadian sleep problems, as recently reviewed by Coogan (Coogan et al., 2016). In particular, delayed sleep phase syndrome (DSPS) and late chronotype are frequently comorbid in adults with ADHD (American Psychiatric Association, 2013; Bron et al., 2016, Kooij and Bijlenga, 2013) and adolescents with ADHD (Sivertsen et al., 2015). Individuals with DSPS have sleep onset insomnia if they try to go to sleep early: sleep-onset is usually after midnight, with consequent difficulty awaking, daytime sleepiness and impaired functioning. The duration of symptoms is at least 6 months (American Psychiatric Association, 2013). Chronic sleep deprivation and short sleep duration have also been associated with ADHD (Hysing et al., 2015).

A subject's chronotype refers to the behavioral manifestation of underlying circadian rhythms, as evidenced by regular rising and sleep-onset times during 24 h (Roenneberg et al., 2003). Chronotype, regulated by the biological clock in the suprachiasmatic nuclei (SCN), consists of morning, evening and intermediate types (Adan et al., 2012). Timing of sleep and wakefulness may differ during work and free days, as sleep deficit accumulates during working days, but is compensated for on free days, when rising time is later (Groeger et al., 2004). Phase and duration of sleep on *free* days are believed to reflect circadian rhythm most accurately as there are fewer externally enforced schedules (Roenneberg et al., 2003). Adults with ADHD are often evening types, up to 78% have initial insomnia if they go to bed early; and initial insomnia in ADHD is associated with a delayed secretion of the sleep hormone, melatonin (van Veen et al., 2010).

SAD and DSPS appear to be overlapping conditions in terms of clinical presentation and comorbidity (Lewy et al., 2006; Oyane et al., 2008). Both may result from "phase shifts" in the circadian rhythm. For most SAD patients, it is argued that a phase shift occurs during winter, when the dawn occurs later. Here, the natural daily rhythms of light are out of phase with the patient's sleep/wake cycle, and hence, this cycle is delayed (Lewy et al., 2006). Therefore, depression occurs in winter when the photoperiods become shorter. Recovery is induced with increasing exposure to sunlight in spring (Rohan and Haaga, 2009). In DSPS, the late sleep-onset reflects an inability to regulate to the external cue of diminished light, resulting in a phase delay (Kim et al., 2013).

Several mechanisms for the relationship between disturbed sleep and ADHD have been explored (Hvolby, 2015). Sleep disturbance in ADHD may result from nocturnal hyperactivity, where stimulant treatment may ameliorate sleep (Hvolby, 2015). Alternatively, sleep problems may precipitate the behavioral and cognitive symptoms of ADHD. This interaction between ADHD and sleep disturbance has been elegantly depicted as a feed-forward loop, where sleep problems cause neurobehavioral morbidity in ADHD, and ADHD results in the sleep problems associated with its comorbid disorders, depression and anxiety (Hvolby, 2015).

ADHD, DSPS and SAD share features which suggest they are all disorders of the biological rhythm. The mechanism underlying the circadian rhythm disturbance in ADHD is unclear, but a recent animal model showed that disruption of a circadian clock gene elicits an ADHD-like syndrome, with alteration in dopamine levels (Huang et al., 2015). Body temperature changes and delayed melatonin secretion are also implicated in ADHD (Bijlenga et al., 2013b; van Veen et al., 2010). In winter, SAD and DSPS present with low mood (Lee et al., 2011) and problems synchronizing to external cues such as daylight, especially when these cues are weak. In terms of treatment, symptom of ADHD, SAD and DSPS improve when therapy involves 'phase resetting'. Both DSPS and SAD respond to morning bright light therapy and/or evening melatonin administration (Lewy et al., 2006; Rahman et al., 2010). In an open study of patients with ADHD and SAD, core ADHD symptoms improved when remediated with light therapy (Rybak et al., 2006). Finally, the three conditions may have shared genetic factors (Baird et al., 2012). ADHD is highly heritable (Hawi et al., 2015) and evidence points to underlying polymorphisms in clock genes in all three disorders (Coogan et al., 2016). This comorbidity and shared genetic etiology may explain the symptomatic overlap of ADHD, SAD and DSPS.

However, to our knowledge, only one study has investigated all three conditions. Bijlenga and colleagues found an association between ADHD, late sleep and seasonal depressive symptoms (Bijlenga et al., 2013a) and our prior study showed that ADHD symptoms add risk to circadian rhythm sleep problems in depression and anxiety (Bron et al., 2016). Our aim in this study was to add new knowledge about the relationships between these disorders. Specifically, we investigated whether indicators of a delayed circadian rhythm (sleep-onset and offset times, mid-sleep) as well as short sleep duration, mediated in the relationship between ADHD symptoms and seasonal depressive symptoms. If indeed circadian rhythm plays a role in the high prevalence of SAD in ADHD patients, then effective treatments could ameliorate symptoms of both disorders in this group (Kooij and Bijlenga, 2013). Improving mood and sleep disorders may well decrease health resource utilization and improve quality of life in ADHD (Kawatkar et al., 2014).

2. Method

2.1. Participants

Subjects participated in the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal, naturalistic cohort study of 2981 participants, aged 18–65 years. Participants were recruited from different health care settings (community, primary and specialized mental health care) and included a group without psychiatric symptoms ('Controls') and others with current and remitted affective disorders. A full description of NESDA has been reported elsewhere (Penninx et al., 2008). Ethical Review Boards of all participating centres approved the NESDA study protocol and it was carried out in accordance with the latest Declaration of Helsinki. All participants gave written informed consent at enrolment after the study procedures had been fully explained. All measures in this study were taken from the 2-year follow-up assessment of NESDA, except the assessment of ADHD symptoms, (performed at the 4-year follow-up). Subjects included were those participating in both of these follow-up visits (2239 respondents, 75.1% of the total sample).

2.2. ADHD symptoms

To identify clinically significant ADHD symptoms, the Conners Adult ADHD Adult Rating Scale–Self report: Screening Version (CAARS-S:SV) was used at the 4-year follow-up assessment. The CAARS-S:SV is a 30-item questionnaire that assesses ADHD symptoms and behaviors. The 18-item Total symptom scale identifies the presence of DSM-IV criteria for ADHD (range of possible scores 0–54) (American Psychiatric Association, 2013). The CAARS-S:SV uses a 4-point Likert-scale format in which respondents are asked to rate items pertaining to current behavior and problems. Ratings range from 0 (not at all, never) to 3 (very much, very frequently). The validity and reliability of the CAARS-S:SV have been confirmed