

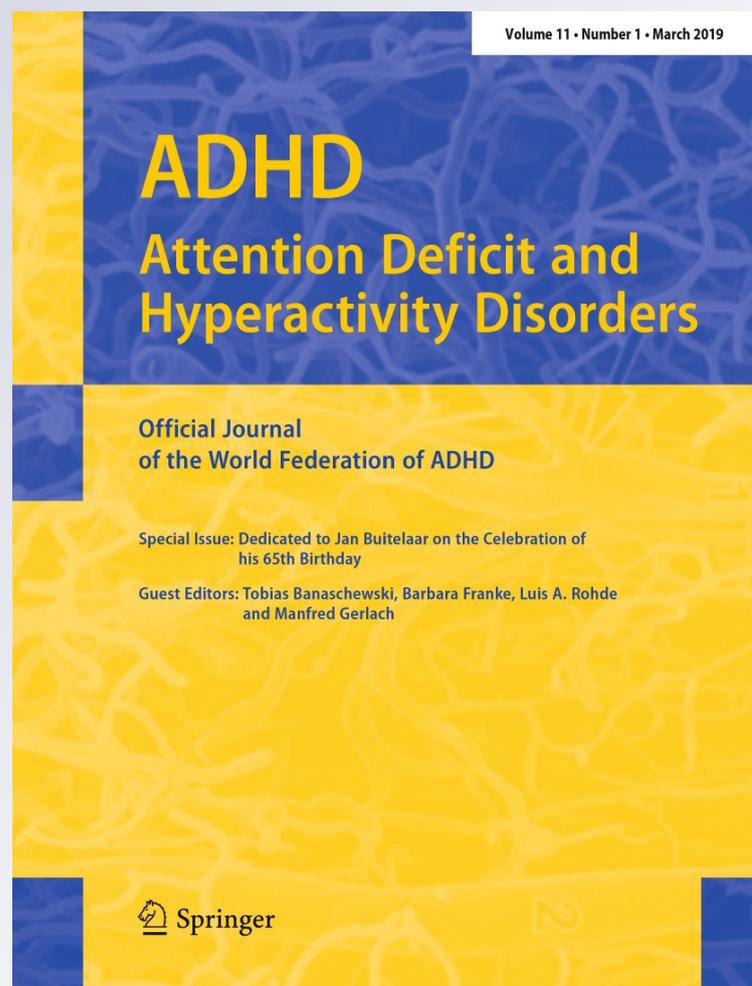
# *The role of the circadian system in the etiology and pathophysiology of ADHD: time to redefine ADHD?*

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# The role of the circadian system in the etiology and pathophysiology of ADHD: time to redefine ADHD?

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## Abstract

Attention-deficit/hyperactivity disorder (ADHD) is highly associated with the delayed sleep phase disorder, a circadian rhythm sleep–wake disorder, which is prevalent in 73–78% of children and adults with ADHD. Besides the delayed sleep phase disorder, various other sleep disorders accompany ADHD, both in children and in adults. ADHD is either the cause or the consequence of sleep disturbances, or they may have a shared etiological and genetic background. In this review, we present an overview of the current knowledge on the relationship between the circadian rhythm, sleep disorders, and ADHD. We also discuss the various pathways explaining the connection between ADHD symptoms and delayed sleep, ranging from genetics, behavioral aspects, daylight exposure, to the functioning of the eye. The treatment options discussed are focused on improvement of sleep quality, quantity, and phase-resetting, by means of improving sleep hygiene, chronotherapy, treatment of specific sleep disorders, and by strengthening certain neuronal networks involved in sleep, e.g., by sensorimotor rhythm neurofeedback. Ultimately, the main question is addressed: whether ADHD needs to be redefined. We propose a novel view on ADHD, where a part of the ADHD symptoms are the result of chronic sleep disorders, with most evidence for the delayed circadian rhythm as the underlying mechanism. This substantial subgroup should receive treatment of the sleep disorder in addition to ADHD symptom treatment.

**Keywords** ADHD · Delayed sleep · Circadian rhythm · Sleep-onset insomnia · Sleep disorders

## Introduction

Sleep problems are often regarded as a comorbidity in psychiatric disorders. Since the first publications on the connection between sleep problems and attention-deficit/hyperactivity disorder (ADHD) in the early 1970s (Conners 1970),

many studies have followed. In the past decade, knowledge has moved ahead more quickly with many pivotal publications on this topic. Recent systematic reviews by Diaz-Roman et al. showed that there is an association between ADHD and both subjective and objective sleep disturbances in both children and in adults (Diaz-Roman et al. 2016, 2018). Another recent systematic review of 22 studies by Coogan and McGowan (2017) showed consistent evidence for the association between ADHD and a later chronotype or a delayed sleep. One study even implicated a causative role of the circadian rhythm and sleep problems in a subgroup of patients with ADHD (Arns and Kenemans 2014).

This review aims to present the current insights into the role of the circadian rhythm and sleep in ADHD, and an overview of past and recent studies on this topic. The first paragraphs give a general introduction to the basic science of sleep, circadian rhythm, and the consequences of sleep and circadian rhythm problems. From there, the genetic, etiological, and functional connection between ADHD circadian rhythm misalignment and sleep problems is discussed. The final paragraphs focus on diagnostic, treatment,

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and prevention possibilities, and recommendations for future studies. Ultimately, we evaluate whether the time has come to redefine the current view on ADHD. We present our hypothesis, based on the current insights, stating that in patients with ADHD, at least a part of the symptoms of ADHD are the result of chronic sleep disorders, with most evidence for the delayed circadian rhythm as the underlying mechanism.

## Sleep basics

Humans spend about one-third of their lives in a sleeping state, although the function and implications of this 'inactive state' are not fully understood to date. However, we do know what happens if we don't sleep. From case studies and experiments, it is known that sleep is needed for the restoration of bodily functions, memory consolidation, and elevation of mood, cognitive function, and general health, and plausibly for healthy brain development (Kurth et al. 2016). In this paragraph, some of the basics of sleep science are elaborated.

## The two-process model

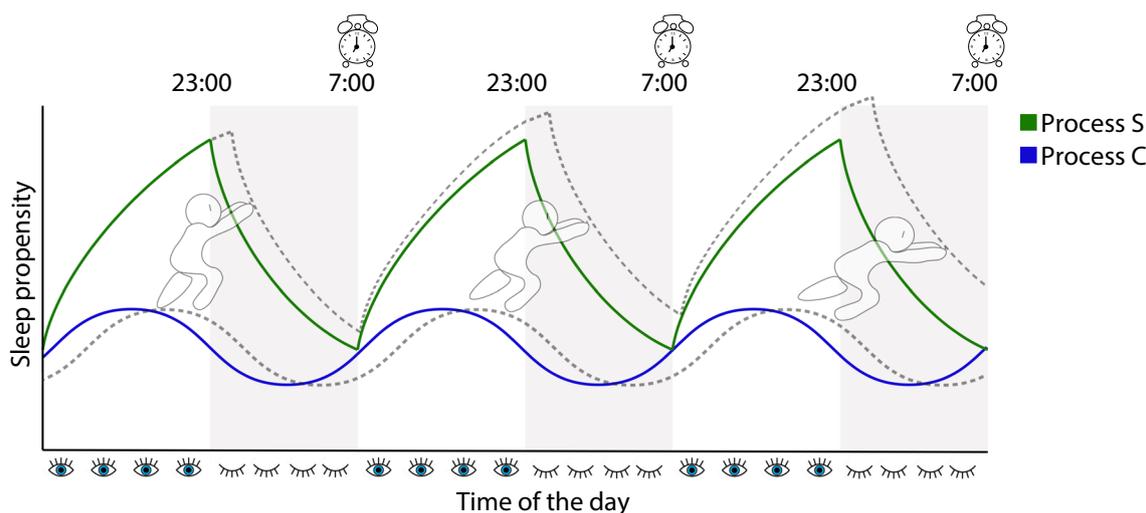
A well-known, validated, and accepted model in sleep medicine is the two-process model by Borbély (1982). This model postulates the sleep pressure Process-S and the circadian Process-C, see Fig. 1. Both Process-S and Process-C, and especially their interaction, play a crucial role in sleep-wake regulation and optimal vigilance (i.e., alertness) regulation. Throughout this review, the two-process model of sleep will be used to explain some of the mechanisms involved in sleep deprivation and disorders.

Process-S reflects the increase in *sleep pressure*, or drowsiness, and is a function of the duration of wakefulness which starts accumulating after waking up in the morning (Achermann et al. 1993). This drowsiness can be quantified using the electroencephalogram (EEG) and is often reflected as frontal theta activity, a slow EEG rhythm (Arns and Kene-mans 2014). This slow theta activity builds up during the day and shows a gradual decline during sleep.

The *circadian* Process-C reflects the individuals' biological clock, which fluctuates with a cycle of about 24 h (hence the term 'circadian'). Figure 1 depicts how processes S and C interact. The larger the distance between processes S and C, the higher the sleep pressure, indicating the most likely moment of sleep initiation.

## Sleep stages

Normal sleep consists of several consecutive sleep stages that occur in a cyclic pattern of approximately 90 min per sleep cycle. The most widely used guidelines for the definition of sleep stages are those by the American Academy of Sleep Medicine (AASM) (Berry et al. 2015). The AASM recommends the subdivision of the following sleep stages: REM (rapid eye movement), N1 (non-REM stage 1), N2, and N3, where N1–N3 is graded from light to deep sleep respectively. N1 is also referred to as drowsiness or shallow sleep and is characterized by low-amplitude and mixed frequency brain activity as quantified by EEG. N2 is the transition phase from N1 to N3 and is characterized by the typical N1 EEG signal, plus short bouts of high-voltage activity or high amplitude (sleep spindles and K-complexes, respectively). N3 is the deep sleep phase, which is characterized by high-amplitude slow wave EEG. The REM sleep phase is



**Fig. 1** The two-process model of sleep, of a normal (green and blue) and a delayed circadian rhythm (dotted lines). Process S indicates sleep pressure; Process C indicates the circadian rhythm

distinguished by low muscle tone (except for the tiny muscles such as present in the eye) and is also referred to as the 'dream' phase of sleep.

From the start to the end of a night's sleep, the relative amount of time spent in N3 (deep) sleep declines per cycle, while the relative duration of REM sleep increases over the sleep cycles. The first one or two sleep cycles are therefore regarded as 'restorative' sleep, while the last sleep cycles are more dominated by dreaming. Sleep also changes over the course of life. In a meta-analysis of 65 studies among 3577 healthy sleepers from age 5 up to 102 years old, it was reported that time spent in sleep stadia N1 and N2 increases with age, while time in N3 and REM sleep decreases (Ohayon et al. 2004).

### Circadian rhythm and chronotype

Many people are known as typical 'morning' or 'evening' people, also referred to as chronotypes, but most people fall in between these chronotypes (Roenneberg et al. 2003). A person's chronotype is to a large part genetically determined (Brown et al. 2008). Chronotype can alter somewhat over the lifespan and differs most between genders in adolescence (Paine et al. 2006; Roenneberg et al. 2004). For instance, a higher percentage of adolescents are classified as evening chronotype relative to adults, of which more boys than girls (Roenneberg et al. 2003). Among the general population, 2–26% of adults are evening chronotypes (Paine et al. 2006; Taillard et al. 2004). This wide prevalence range is due to the different age ranges examined and to the different methods used for assessment of chronotype.

The circadian rhythm is regulated by the suprachiasmatic nuclei (SCN) in the brain. The SCN synchronizes to endogenous clock signals such as various hormonal statuses and to the external environment making use of so-called zeitgebers, such as daylight, environmental temperature, and food availability (Roenneberg et al. 2007). A crucial zeitgeber is daylight intensity reaching the retina of the eye, which gives the SCN information about the time of the day, thereby leading to photoentrainment of the internal clock system.

The SCN orchestrates many complex 'timed' internal systems such as body temperature, endocrine functions, and blood pressure through autonomous rhythms. The individual's sleep/wake cycle is also directed by the SCN. Internal and external zeitgebers are translated to information about the time of the day by the SCN. Human photoentrainment is predominantly linked to dusk (Kantermann et al. 2007), when daylight intensity is diminished and its color spectrum shifts from blue to red. That is when the SCN signals the pineal gland to produce melatonin, the 'sleep hormone' (Benarroch 2011). The rise of the endogenous melatonin concentration is often used as the phase marker of the circadian rhythm (Process-C in Fig. 1) and can be measured

in blood and saliva. The time of the day that the melatonin concentration in saliva reaches the threshold of 3 pg/ml is termed the dim-light melatonin onset (DLMO) (Lewy and Sack 1989). Sleep is typically initiated 2–3 h after the time of DLMO (Lewy 2007). The most widely used biomarkers for the circadian phase are the DLMO, the core-body temperature, and objective actigraphy measures.

### Impact of sleep disturbances

Disturbance of sleep can have consequences, as we all experience at least occasionally. While occasional sleep *deprivation* is evident to have detrimental effects on cognitive functioning (Slama et al. 2017), comparable effects have been found after sustained sleep *restriction* (Van Dongen et al. 2003), i.e., limiting the amount of time in bed. In a sleep restriction study, participants were allowed to sleep for 6 h for 2 weeks, which led to a decline of sustained attention and working memory that was equal to two nights of *complete sleep deprivation*. In contrast to participants that were sleep-deprived, sleep-restricted participants were unaware of their cognitive deficits. Similar findings have been reported after 5–7 days of sleep restriction (Axelsson et al. 2008; Belenky et al. 2003). These studies also showed that these cognitive deficits, most specifically inattention, needed more days of normal sleep in order to fully recover than the duration of the initial sleep restriction (Axelsson et al. 2008; Belenky et al. 2003). Sleep restriction studies have also been conducted in children, albeit not as extensively as in adults. In general, sleep restriction studies in healthy children have demonstrated impairments of attention (Fallone et al. 2001, 2005; Sadeh et al. 2003; Beebe et al. 2008) and more impaired behavior regulation after 1 week of sleep restriction (Belenky et al. 2003). Thus, core symptoms of ADHD such as inattention and externalizing behavior can be induced in healthy children through sleep restriction (Fallone et al. 2001; Golan et al. 2004), suggesting a role for chronic sleep debt in the etiology of ADHD.

In a meta-analysis of 12 studies on 35,936 healthy children between 5 and 12 years of age, Astill and colleagues (Astill et al. 2012) demonstrated clear associations between longer sleep duration and better executive function and school performances, and also between shorter sleep and more internalizing and externalizing behavior problems. Also adolescents that go to bed late have lower school performances (Zerbini and Merrow 2017). Several studies demonstrated that when morning school-time was delayed by half an hour, sleep duration increased by 29–45 min, with subsequent reductions in daytime sleepiness, depressed mood and caffeine use (Boergers et al. 2014; Owens et al. 2010). In a multicenter study among 9000 students, it was even shown that when school started 90 min later (a shift

from 7.35 to 8.55 am), the number of car crashes among teen drivers reduced by 70% (Wahlstrom et al. 2014).

A systematic review with data on 690,747 children from 20 countries showed that children nowadays on average sleep 1 h and 15 min less than a century ago (Matricciani et al. 2012) and thus may be for a larger part chronically sleep-restricted. It seems that children and adolescents today generally sleep too short, supported by a trend for increased signs of drowsiness in healthy children over 10 years' time, as objectified using EEG (Arns et al. 2013a) (reflecting Process-S, depicted in Fig. 1).

## Sleep and circadian rhythm in ADHD

In non-experimental settings, sleep disturbance is associated with behavioral characteristics of ADHD in both healthy individuals (Kass et al. 2003; Gau et al. 2007) and non-medicated individuals diagnosed with ADHD (Mahajan et al. 2010). In the following paragraphs, these associations will be further discussed.

### Sleep disorders associated with ADHD

In children with ADHD, there is a vast amount of literature on the increased prevalence of various sleep disorders and sleep problems, including delayed sleep–wake disorder, insomnia, sleep-disordered breathing, increased nocturnal motor activity, restless legs, and parasomnias such as sleep anxiety and teeth clenching (Van der Heijden et al. 2005a, b; Tsai et al. 2016; Mota-Veloso et al. 2017; Melegari et al. 2016). Furthermore, a systematic review showed that children with ADHD spend relatively more time in N1 (shallow) sleep as compared to controls (Diaz-Roman et al. 2016). As a result of the lower sleep quality, children with ADHD have increased daytime sleepiness (Velez-Galarraga et al. 2016; Craig et al. 2017). Moreover, the severity of sleep problems was correlated to poorer cognitive functioning in children with ADHD (Sciberras et al. 2015). Of the adolescents with ADHD, 73% reports any sleep problem, and 42% has daytime sleepiness (Langberg et al. 2017; Hysing et al. 2016). Finally, among adolescents from the general population, more ADHD symptoms were associated with more delayed sleep, shorter sleep, longer time awake before falling asleep, more nocturnal wake time, higher sleep deficiency, and more insomnia (Hysing et al. 2016).

In adults with ADHD, sleep is also affected: 78% of them have a delayed circadian rhythm as objectively measured by actigraphy and DLMO, and an increased prevalence of short sleep as compared to healthy controls (van Veen et al. 2010; Bijlenga et al. 2013a). The Restless Legs Syndrome (RLS) is prevalent among 35–44%, and insomnia in 67% of adults with ADHD (Cortese et al. 2005; Snitselaar et al.

2015; Brevik et al. 2017). The prevalence of sleep apnea in adults with ADHD has not been established yet, but there are indications that symptoms of sleep apnea are related to ADHD symptoms (Vogel et al. 2017). For example, in sleep medicine it is taught that a cardinal feature of sleep apnea is hyperactive behavior during the day. There are also more symptoms of sleep apnea in those with ADHD as compared to controls (Bjorvatn et al. 2017). A recent longitudinal twin study showed that children with ADHD had poorer sleep quality in young adulthood, but only if their ADHD persisted (Gregory et al. 2017). Conversely, the severity of sleep problems in children with ADHD is an important predictor for the persistence of ADHD into young adulthood (Cadman et al. 2016). The two thus seem intimately intertwined across the lifespan in individuals with ADHD.

A few studies in children have reported a decrease of ADHD symptoms after treatment of specific sleep problems and disorders. These included a sleep coaching intervention for sleep-onset insomnia (Corkum et al. 2016), treatment of sleep apnea by removal of the adenoid and tonsils (Huang et al. 2007), or dopaminergic therapy for restless legs syndrome (Walters et al. 2000), suggestive of a more causative relation between the ADHD symptoms and the present sleep disorder.

The relationship between sleep problems and the two symptom domains of ADHD is not clear yet. Some studies report a relationship between sleep problems and symptoms of hyperactivity/impulsivity (Bijlenga et al. 2013a; McGowan et al. 2016), but a meta-analysis including 13 studies relates sleep problems mainly to symptoms of inattention (Lundahl et al. 2015). Our previous population study links sleep problems to both symptom domains (Vogel et al. xxxx).

### Circadian rhythm and ADHD symptoms

Of all sleep problems associated with ADHD, a delayed sleep/wake cycle is the most common (i.e., a delayed circadian rhythm) (Coogan and McGowan 2017; Snitselaar et al. 2017; Kooij and Bijlenga 2013), with an objectively measured prevalence of 73–78% in both children and adults with ADHD (Craig et al. 2017; van Veen et al. 2010). Following Fig. 1, a delayed Process-C 'pushes' Process-S, resulting in a delayed sleep propensity and later sleep. Waking up at regular times results in shorter sleep, non-restored sleep propensity (i.e., daytime sleepiness), and accumulated sleep propensity over the days. Eventually, a chronically delayed rhythm will 'push' Process-S to the limit, resulting in mental and physical complaints. This is similar to the impaired attention and executive function as a potential result of the delayed rhythm and subsequent sleep restriction seen in this population. While many people from the general population have an evening chronotype, only just 0.1–3.1% fulfills

diagnostic criteria for the delayed sleep phase syndrome (DSPS) (Yazaki et al. 1999; Schrader et al. 1993; Sivertsen et al. 2013). According to self-reports, the DSPS prevalence in adults with ADHD is at least 26%, which is a huge increase as compared to the general population (Bijlenga et al. 2013a). Other studies have investigated the occurrence of sleep-onset insomnia (SOI), which is difficulty falling asleep and/or a sleep-onset latency of more than 30 min. In the literature, SOI and DSPS are both used to characterize a delayed circadian rhythm in adults with ADHD. SOI is present in 72–78% of non-medicated children and adults with ADHD, using DLMO as the objective circadian marker (Van der Heijden et al. 2005b; Van Veen et al. 2010). In another study, we found that the time span between DLMO and sleep initiation was on average about an hour longer in those with ADHD and a delayed circadian rhythm, as compared to healthy controls (Bijlenga et al. 2013b). This trend is also confirmed from subjective reports, where 57% of adults and children with ADHD had SOI compared to 18% in controls (Arns et al. 2014a). This may indicate lower synaptic sensitivity to melatonin and/or perhaps a behavioral aspect leading to sleep procrastination.

### The link between sleep problems and ADHD

The functional and neuroanatomical overlap between brain regions involved in attention, arousal, and sleep regulation reflects the complex relationship between ADHD and sleep (Owens 2008). Sleep problems may be causes, effects, or intrinsic features of ADHD (Hvolby 2015).

For instance, in young children we are all familiar with the hyperactive, ‘high-spirited’ behavior when they are very tired. These children compensate for their fatigue with hyperactive behavior (O’Brien 2009; Hegerl and Hensch 2014). In this example, hyperactivity is caused by sleepiness and is regarded as a vigilance autostabilization behavior (i.e., keeping yourself awake by moving/talking). A healthy adult experiencing drowsiness at home near bedtime will feel sleepy and will decide to ‘withdraw,’ seeking an environment with low external stimulation, thus increasing the probability of falling asleep. However, when this same healthy adult is driving a car experiencing the same drowsiness, he will try to avoid further drowsiness by turning up the volume of the radio, open the window and lower the temperature by turning down the heating, and so on. Hence, this healthy person will exhibit autostabilization or externalizing behavior in order to stay awake. This autostabilization behavior can thus be either adaptive (i.e., keeping oneself awake while driving a car) or maladaptive (i.e., the hyperactivity in children with ADHD and the constant mind wandering in adults with ADHD), depending on the circumstance and chronicity.

However, hyperactive behavior in the evening may also be the *cause* of sleep-onset problems (Cortese et al. 2009).

A child exhibiting hyperactive behavior in the evening may seem full of energy and thus postpone bedtime. Also, adults may experience internal hyperactivity such as internal restlessness, many thoughts, or rumination that keeps them awake.

Another link between sleep and ADHD is that sleep disorders may also lead to symptoms, behaviors or functional impairments that mimic those in ADHD, such as concentration problems, learning impairment, problematic behavior, and emotion dysregulation (O’Brien 2009). This points to the direction that sleep problems and ADHD share intrinsic features. In a recent study among healthy individuals, the trait impulsivity was associated with objective measures of phase delay, lower sleep quality and sleep efficiency (McGowan and Coogan 2018). Furthermore, medical treatment of ADHD also impacts sleep, with limited evidence for both positive effects in children (Owens et al. 2016) and adults (Kooij et al. 2001), and negative effects in children (Becker et al. 2016; Santisteban et al. 2014). Moreover, children with ADHD with a longer sleep duration before the start of their treatment have a higher chance of better treatment response (Morash-Conway et al. 2017).

The delayed circadian rhythm and ADHD have genetic associations and shared environmental factors, and may have shared etiology. Other sleep problems may also contribute to the severity of ADHD symptoms. All of these factors interact and influence each other. An important environmental factor is exposure at night to blue light sources such as LED lights and the use of light-emitting sources such as smartphones or tablets (Chaste et al. 2011; Baird et al. 2011; Bijlenga et al. 2011; Arns et al. 2013b, c), for review see (Roenneberg and Merrow 2016). Using smartphone data, researchers found that social media activities delayed bedtimes and led to shorter sleep duration (Walch et al. 2016). This may be explained by both the effect of the light emitted by the smartphone, and also by postponing sleep because of arousal from engagement in the social media activities.

Sleep problems that emerged in childhood may have had functional and neuronal consequences, for neuronal networks involved in sleep, sleep behavior, and for persistence of the ADHD symptoms in later life (Kurth et al. 2016). In order to understand the consequences of sleep problems in early childhood, longitudinal studies are needed that focus on the functional and behavioral effects of chronic sleep problems. While a minority of all patients diagnosed with ADHD do not experience sleep problems, the proposed hypothesis holds for the (larger) subgroup of patients with ADHD that has sleep problems.

### Genetics

The heritability of chronotype is estimated to be approximately 50% (Kalmbach et al. 2017). Across three important

genome-wide association studies (GWAS), nine genes were identified that are responsible for morningness (Jones et al. 2016; Lane et al. 2016; Hu et al. 2016), reviewed in Kalmbach et al. (2017). For the identification of genes responsible for eveningness, however, only candidate-gene studies have been performed thus far. Some of the variations in genes that are responsible for a lengthening of the sleep/wake cycle, resulting in a longer than 24-h circadian rhythm (Process-C, Fig. 1) and thus a delayed sleep, have also been linked to ADHD (Coogan and McGowan 2017; Baird et al. 2012; Xu et al. 2010). One of these is the CLOCK gene, which has been linked to ADHD, bipolar, and depressive disorder (Coogan and McGowan 2017; Xu et al. 2010; Benedetti et al. 2003). The BMAL1 and PER2 genes are also involved in both delayed sleep and in ADHD: both genes showed decreased circadian rhythmicity in ADHD subjects as compared to healthy adults (Baird et al. 2012). The alleles upstream from PAX8 are associated with sleep duration and with thyroid function, and less copies of the minor alleles are associated with both shorter sleep duration and with ADHD symptoms (Gottlieb et al. 2015).

### Solar intensity and ADHD

Late chronotypes have significant variation in their average sleep duration across the year, especially from the end of March until end of October, i.e., during Daylight Saving Time (DST) they sleep less, while earlier chronotypes do not (Allebrandt et al. 2014). Intense natural light in the morning counteracts phase-delaying effects (Lewy et al. 1987). People that are typically exposed to outdoor (natural) light go to sleep earlier, and sleep more than those typically exposed to indoor (non-natural) light (Walch et al. 2016). A delayed circadian phase was advanced by morning bright light therapy in two pilot studies among adults with ADHD (Fargason et al. 2017; Rybak et al. 2006). Consistent with this, Arns et al. found that among people without Northern (i.e., Scandinavian) genetic background (hypothesized to be less susceptible to variation in sunlight intensity, as discussed in Arns et al. 2015), there is a strong geographical correlation between higher solar intensity and a lower prevalence of ADHD (Arns et al. 2013b, 2014b). This relationship is explained by the fact that sunlight intensity serves as an important cue for the brain's circadian rhythm regulation, where high daylight intensity is a stronger cue than low daylight intensity to synchronize the circadian rhythm that also improves deep sleep (Lewy 2007; Roenneberg et al. 2007; Wams et al. 2017). Those with a genetic disposition to a lengthening of the sleep cycle may therefore profit from stronger synchronization cues such as high daylight intensity as well as dark evenings and nights, leading to a better synchronized circadian rhythm, better sleep, and less ADHD symptoms.

There are indications that there is an early 'imprint' or programming of the biological clock relative to light intensity or day length, which occurs in the weeks or months after birth. In mice, exposure to light in the perinatal period determines the responsiveness of its biological clock to subsequent changes in day length changes (i.e., changes of the 'photoperiod') (Ciarleglio et al. 2011). Also in laboratory studies in humans, there are indications of an adaptation of the circadian system according to prior light exposure (Chang et al. 2011). Besides the genetic makeup, the season of birth may also influence the development of one's circadian system. Indeed, the prevalence of evening chronotypes in healthy individuals born in June and July is highest and lowest in December and January (Natale and Adan 1999; Natale et al. 2002), reviewed in Brooks and Canal 2013). Another study demonstrated that adolescents born in months associated with an increasing day length were later chronotypes than those born in months with decreasing day lengths (Vollmer et al. 2012). When the prevalence of ADHD was studied in relation to season of birth, Seeger et al. (2004) reported that being a 7R carrier of dopamine D4 receptors (one of the genetic risk factors associated with ADHD) (Nikolaidis and Gray 2010), and being born in spring or summer resulted in a 2.8 higher likelihood of being diagnosed with 'hyperkinetic disorder' (i.e., ADHD). However, in a much larger study, the hypothesized association between season of birth and ADHD was refuted after adjustment for multiple testing (Brookes et al. 2008). A note on the latter study, however, may be that the majority of the included subjects had a Northern genetic background (who are hypothesized to be less susceptible to variation in sunlight intensity, as discussed in Arns et al. 2015). This intriguing link is currently being investigated in more detail by the authors (Vollebregt and Arns 2016).

### The role of the visual system

There are several studies indicating that the visual system in ADHD is also affected. In children with ADHD, 76% has reduced visual acuity, i.e., more strabismus (cross-eyedness), subnormal stereo-acuity (depth detection), convergence insufficiency, and/or smaller optic disks (Gronlund et al. 2007). The incidence of ADHD was threefold within a group of children having convergence insufficiency as compared to the general US population (Granet et al. 2005; Barnhardt et al. 2012). Another indication for visual system abnormalities in ADHD is the prevalence of as much as 83% of refractive errors in children with ADHD (Mezer and Wagnanski-Jaffe 2012). Furthermore, young adults with ADHD have more problems with depth perception, peripheral vision, and color perception, especially in the blue spectrum, as compared to matched controls (Kim et al. 2014; Banaschewski et al. 2006). Moreover, abnormalities in the visual field and

the visual acuity in children with ADHD improved with ADHD medication (Martin et al. 2008). In another study, children with strabismus and increased ADHD symptoms had less ADHD symptoms after strabismus surgery, a result that gives rise to the idea that the eye problems caused or aggravated the ADHD symptoms in these children (Chung et al. 2012).

Besides the well-known rods and cones photoreceptor cells in the retina that are responsible for night and color vision, there are also retinal photoreceptor cells that are responsible for the non-image forming perception of light intensity. These are the M1-type intrinsically photosensitive retinal ganglion cells (ipRGCs), which modulate, among others, the pupillary reflex, the release of melatonin and dopamine, and project via the retinohypothalamic tract to the suprachiasmatic nuclei (SCN) (Schmidt and Kofuji 2009). Dopamine is released during daytime and inhibits melatonin secretion, and vice versa, melatonin is released in the evening and night and inhibits dopamine release (Stone et al. 2013). The photopigment melanopsin in these ipRGCs is most sensitive to blue light wavelengths (Lockley et al. 2003; Provencio et al. 2000). In addition to projection to the SCN, the ipRGCs also project to sleep-promoting neurons in the ventrolateral preoptic nucleus and superior colliculus (Lupi et al. 2008). The SCN synchronizes multiple peripheral clocks that will together drive circadian rhythmicity (Meijer et al. 2007).

The first studies linking ipRGC functioning to psychiatric disorders are relatively new. Roecklein et al. showed that patients with seasonal affective disorder (SAD) ('winter depression') had deviant ipRGC functioning compared to controls (Roecklein et al. 2013a, b). The SAD patients had a reduced pupil dilation after exposure to blue light, but not after red light. Roecklein et al. hypothesized that their SAD patients have a decreased blue-spectrum light sensitivity, which is responsible for a weaker circadian entrainment of the SCN to natural daylight. This could have triggered the depression during wintertime when natural daylight intensity is diminished. The prevalence of SAD is almost ten times as high among adults with ADHD as compared to the general population (Mersch et al. 1999; Amons et al. 2006). The functioning of the ipRGCs is hypothesized also to be sub-optimal in ADHD. In our preliminary web survey, 69% of adults with ADHD reported oversensitivity of their eyes to bright light, versus 24% in those without ADHD (Kooij and Bijlenga 2014). Respondents with ADHD also reported to wear sunglasses significantly more hours during all seasons as compared to the control group, thereby possibly further compromising synchronization of the biological clock to daylight. This result supported the idea that the oversensitivity to light in the ADHD population reflects a deviant retinal development or functioning. This hypothesis is currently

under further investigation by the authors, see the online Dutch trial register [www.trialregister.nl](http://www.trialregister.nl), #NTR4337.

## Retinal dopamine and melatonin

The ipRGCs have connections with the amacrine cells that produce dopamine, also located in the retina (Stone et al. 2013; Mendoza and Challet 2014). Retinal dopamine dysfunctioning has been hypothesized to play a role in the regulation of neurodevelopmental growth of the eye, leading to refractive errors, which may explain the increased prevalence of refractive errors that were found in ADHD (Mezer and Wygnanski-Jaffe 2012; Stone et al. 2013). Interestingly, ADHD is considered a neurodevelopmental disorder that is associated with low dopamine levels in certain brain areas (Sikstrom and Soderlund 2007), and the retina is basically an outgrowth of brain tissue (Erskine and Herrera 2014). The dopaminergic DRD4 gene is heavily involved in converting light to electrical signals in the retina, and its transcription exhibits a strong circadian pattern in rodents (Kim et al. 2010). A DRD4 7R allele is one of the proposed genetic risk factors of ADHD (Nikolaidis and Gray 2010). Compared to other DRD4 genotypes, carriers of the 7R genotype have less ability to reduce the light-sensitive second messenger cyclic adenosine monophosphate (cAMP) level with illumination (Asghari et al. 1995). Furthermore, 7R-carriers reported higher daytime sleepiness than non-carriers (Jawinski et al. 2016).

Dopamine and melatonin have opposing roles in the regulation of the circadian rhythm (Mendoza and Challet 2014; Munday et al. 2005; Iuvone et al. 1978). While dopamine is mainly synthesized and released in the early morning and during the day, melatonin is released in the late afternoon or early evening and peaks at night (Iuvone et al. 2005; Doran et al. 1990). Dopamine has an inhibitory effect on melatonin release, and vice versa (Green and Besharse 2004). The dopaminergic system is understood to be under profound circadian control (Parekh et al. 2015), and impaired retinal dopamine synthesis results in circadian rhythm fluctuations (Wirz-Justice 1984). The hypothetically impaired functioning of the ipRGCs in ADHD subgroups may have its reflections on the melatonin and dopamine-producing cells in the retina, thereby having a role in the circadian misalignment as seen in the majority of ADHD patients.

Dopamine also plays a crucial role in sleep regulation. For instance, dopamine neurons in the ventral tegmental area (VTA) have a higher number of active dopamine cells after REM sleep deprivation and during recovery than in normal sleep (Maloney et al. 2002). Given that dopamine plays such a crucial role in the circadian rhythm and sleep regulation, the relationship becomes plausible between specific sleep disorders and a neurodevelopmental disorder associated

with a dysregulated dopamine functioning, such as ADHD (French and Muthusamy 2016).

## Sleep problems and ADHD: two sides of the same coin?

Symptoms of ADHD, a delayed circadian rhythm, and sleep disorders are thus intertwined by various pathways. They seem to share a genetic and etiological background and may profit from a common treatment. However, results from studies investigating such common treatment are yet scarce.

### Importance of recognition and diagnosis

The screening, diagnostic assessment, and treatment of sleep disturbances, besides that of ADHD, is of great importance. Sleep problems and ADHD independently affect the quality of life and social functioning, at least in children (Craig et al. 2017). As the prevalence of sleep disorders is very high in ADHD, those diagnosed with ADHD should be routinely screened for delayed sleep problems and other sleep disorders. Various screening questionnaires are available, such as the Holland Sleep Disorders Questionnaire (HSDQ, also available in other languages including English), which screens for circadian rhythm sleep disorders, sleep-related movement disorders, insomnia, hypersomnia, parasomnia, and sleep-related breathing disorders (Kerkhof et al. 2013). Most patients with ADHD will screen positive for at least the delayed sleep phase disorder (DSPS), which should be followed up by a targeted diagnostic assessment. Besides questions on their sleep times and habits on nights before work days and free days, this may include using objective measures such as wrist actigraphy and/or the determination of the DLMO in saliva for confirmation of a delayed circadian rhythm.

### Treatment options

Treatment of sleep disorders should be conducted alongside the treatment of ADHD and comorbid disorders. Sleep problems associated with mood or anxiety disorders may diminish with the treatment of those disorders. Sleep problems due to a chaotic lifestyle, which is generally characteristic to ADHD, may be reduced by the medical and psychological treatment of ADHD itself. Psycho-education on sleep hygiene may increase awareness of factors affecting sleep and improve the environmental and behavioral aspects that promote better sleep. The preferred treatment for primary insomnia that may also apply for secondary insomnia is a cognitive behavioral treatment for insomnia (CBTi), which encompasses sleep hygiene, stimulus control, sleep restriction, cognitive therapy, and relaxation training.

CBTi is proven highly effective for symptoms of insomnia and improvement of sleep quality, as recently shown in a meta-analysis including 87 randomized controlled trials (van Straten et al. 2018). Moreover, it is safe, has no side effects, and is therefore preferred over sleep medication (Anderson 2018).

### Sleep hygiene

Sleep hygiene consists of lifestyle measures that promote better sleep, such as having a comfortable sleeping area, not using caffeine in the evening, and maintaining a fixed sleep time schedule. Children with ADHD have worse sleep hygiene than controls (van der Heijden et al. 2018), and vice versa a bad sleep hygiene is related to more self-reported sleep problems in adolescents with ADHD (Martin et al. 2018). Sleep hygiene should be part of standard psycho-education in all patients with problems falling asleep, maintaining sleep, early awakening, or low sleep quality (Chen et al. 2010). Sleep hygiene involves directions for the timing and amount of caffeine and use of other substances, how to better entrain the internal circadian rhythm to the external clock time, e.g., by use of bright light in the morning and during the day but not late in the evening or at night, how to increase sleep pressure, e.g., by getting up on time in the morning and exercising, and how to keep the body comfortable enough to be able to sleep, e.g., by increasing skin temperature by taking a shower before bed. An open-label randomized controlled trial among children with ADHD showed that sleep hygiene education significantly decreased sleep problems. More interestingly, the symptoms of ADHD also decreased, and daily functioning and quality of life were increased, up to six months after the intervention (Hiscock et al. 2015). Bad sleep hygiene is however not the only reason why those with ADHD have problems to fall asleep (van der Heijden et al. 2006), as already discussed.

### Chronotherapy

Chronotherapy for a delayed sleep phase involves phase-resetting of the internal clock by the use of exogenous melatonin in the late afternoon or evening, and/or by bright light therapy in the early morning (Kooij and Bijlenga 2013). Melatonin can be used as either a phase-advancing agent in low dosage (e.g., 0.5 mg) in the late afternoon or early evening, or as a sleep-inducing agent in higher dosage (e.g., 3–5 mg) about an hour before bedtime. A meta-analysis of nine studies including adults and children with DSPS showed that melatonin treatment, at various dosages and at various administration times, advanced the DLMO by more than an hour, and the sleep-onset time by 40 min (van Geijlswijk et al. 2010).

An overview on the use of melatonin in pediatric neurology concluded that it is safe and most effective as chronotherapy (Bruni et al. 2015). In 101 children with ADHD and chronic sleep-onset insomnia, treatment during 4 weeks with 3–6 mg of melatonin versus placebo before bedtime, advanced their sleep-onset time with on average 27 min, and increased sleep duration with on average 20 min (Van der Heijden et al. 2007). However, no effect was found on problem behavior, cognitive performance, or quality of life. In the follow-up study after 3.7 years, 65% of these children still used melatonin daily. Of them, 88% reported no sleep-onset problems anymore, 71% reported improved behavior, and 61% reported improved mood (Hoebert et al. 2009). Discontinuation of treatment resulted in a delay of sleep onset in most children, suggesting clinical benefit on ADHD symptoms can be achieved, albeit requires a longer duration of normal sleep.

Light therapy in the morning is indicated as chronotherapy for SAD, which has shown to advance a delayed circadian rhythm as well (Lewy et al. 1984). A small study showed that there is an additive effect of light therapy to the treatment with melatonin alone to advance the circadian rhythm (Paul et al. 2011). Two recent pilot studies also showed promising results for the treatment of ADHD in adults using bright light therapy (Fargason et al. 2017; Rybak et al. 2006). Both studies showed that the improvement in ADHD symptoms was related to the advancement of the circadian rhythm. These results are promising for further investigation in larger studies.

### Treatment of other sleep disorders

Patients with a delayed circadian rhythm can be easily treated by the therapist with chronotherapy. Primary or secondary insomnia symptoms can be treated with CBTi. However, those screened positive for other sleep disorders should be further investigated by specialists in a sleep laboratory. Assessment and treatment of major sleep disorders generally take a few months, and depending on the diagnosis, may range from a behavioral intervention to pharmacological treatment, and even surgery. For example, the treatment of obstructive sleep apnea depends on its cause and may include a posture training, diet, continuous positive airway pressure (CPAP), a tongue-retaining device, and/or surgery in case of physiological malformations underlying the apnea. After the treatment of the sleep disorder, the severity of the ADHD symptoms may be re-evaluated.

### Neurofeedback

Neurofeedback is a method where EEG activity is fed back in real time in order to induce self-regulation over specific brain activity, based on learning principles and operant

conditioning. Several studies have demonstrated that applying this technique for a specific frequency band, namely sensorimotor rhythm neurofeedback (SMR, a 12–15 Hz rhythm found on central lateralized sites) results in increased sleep spindle density during sleep (Sterman et al. 1970; Hoedlmoser et al. 2008), decreased sleep latency (Hoedlmoser et al. 2008), and increased total sleep time (Hoedlmoser et al. 2008; Cortoos et al. 2010). Sleep spindles occur during light and deep sleep where they protect from waking due to external stimuli, thus facilitating the process of falling asleep. After melatonin administration, more sleep spindles are found and a recent polysomnographic study found that children with ADHD exhibited reduced activity in this same 12–15 Hz sigma band during sleep, reflective of reduced sleep spindles (Saletin et al. 2017). Another recent study in a group of ADHD patients showed that SMR neurofeedback resulted in a normalized sleep-onset. Also, those with a normalized sleep-onset latency had improved attention after treatment (Arns et al. 2014a).

SMR neurofeedback is hypothesized to train the sleep spindle network, resulting in long-term potentiation (LTP) that increases synaptic strengths, and the likelihood of future activation of this network (Arns and Kenemans 2014; Sterman and Egner 2006). In line with the finding that cognitive deficits need a period of normal sleep to recover from sleep restriction (Axelsson et al. 2008; Belenky et al. 2003), a recent meta-analysis demonstrated that the effects of neurofeedback on inattention in ADHD further improved to an average of six months after treatment, whereas this was not the case in the non-active control conditions, nor in conditions involving psychostimulant medication treatment (Van Doren et al. 2018).

### Time to redefine ADHD?

In this review we aimed to clarify the link between sleep problems and ADHD symptoms. There are multiple indications that treating those sleep problems reduces ADHD symptoms. The main current scientific consensus is that a dopamine and/or norepinephrine deficit is the neurochemical basis of ADHD that is associated with the main clinical problems of hyperactive, impulsive, and inattentive behavior (e.g., Sharma and Couture 2014). However, ADHD might be better conceptualized as a ‘heterogenous’ disorder from the neurobiological perspective, where at least several subtypes with different etiology exist, most clearly evidenced by the fact that none of the current neurobiological treatments have perfect efficacy. In line with this notion of neurobiological heterogeneity, it makes more sense to aim to explain this neurobiological heterogeneity, in order to develop more specific treatments. We therefore propose a novel hypothesis: ADHD symptoms resulting from a chronic sleep disorder,

with most evidence for the delayed sleep phase disorder, in a large group of patients with ADHD. Chronic circadian sleep disorders that may have a large genetic component, almost always lead to poor sleep quality and/or quantity, with presumed suboptimal development or function of the dopaminergic system and thus to ADHD-like symptoms such as concentration problems, inattention, impulsivity, and hyperactivity. This may also be true for other sleep disorders, but those have been studied less.

However, it is yet unknown whether the (chronic) sleep problems are the sole cause of ADHD symptoms, if there are other underlying mechanisms to the ADHD symptoms, or if the causation in patients is heterogeneous (i.e., the etiology of the ADHD symptoms is different across patients). More research is needed to disentangle these issues and to verify our hypothesis. Future longitudinal studies may investigate the relationship between sleep and ADHD over the course of life.

In line with our hypothesis, we propose an additional diagnostic presentation category referred to as ADHD-SOM (derived from 'somnus,' i.e., sleep). In this group, a part of the ADHD symptoms are the result of chronic sleep disorders.

This suggestion can be embedded in current clinical practice and research. According to the DSM-5, for every diagnosis made, other explanations for the symptoms should be ruled out (APA 2013). We therefore propose clinicians to incorporate assessments that quantify sleep and any sleep problems, thereby ruling those out as the sole cause of the ADHD symptoms. This may be achieved using screening questionnaires such as HSDQ and PSQI, and the assessment of DLMO and/or actigraphy. It is essential to rule out or acknowledge the presence of a circadian rhythm sleep disorder, or sleep disorders such as insomnia, restless legs, or sleep-disordered breathing. When confirmed after further diagnostic assessment, treatment should focus on both ADHD and the sleep problem. The severity of both disorders and the preference of the patient determine the order of the treatments. The assumption that with better sleep, the symptoms of ADHD diminish does not imply that 'standard treatment' of ADHD is less important. When we consider ADHD-SOM as a novel presentation within the diagnosis, sleep treatment, such as chronotherapeutic treatment to get the delayed rhythm stabilized, may be necessary. Our clinical experience tells us that combined ADHD treatment and chronotherapy in ADHD patients with a delayed circadian rhythm adds to better outcomes of the ADHD treatment intervention as a whole, using dopamine supplementation (stimulants) as the 'day agent' and melatonin as the 'night hormone,' as the two naturally have opposing effects with negative feedback loops (Stone et al. 2013). The additive effect of the treatment of any sleep disorder to the ADHD treatment outcomes should be further investigated.

In summary, our plea for a redefinition of part of the ADHD symptoms as the result of a chronic sleep disorder is based on the following pieces of evidence that have been discussed throughout this manuscript:

1. The consistent findings of increased prevalences of various sleep disorders in ADHD populations across studies.
2. Solid scientific evidence for a strong relationship between symptoms of ADHD and a delayed circadian, with 73–78% of patients with ADHD having a delayed circadian rhythm.
3. Sleep restriction studies and cross-sectional studies show that shorter sleep is associated with impaired sustained attention and executive functioning.
4. Genetic associations between ADHD and a delayed circadian rhythm
5. A higher ADHD prevalence in countries and geographical areas with lower solar intensities and thus less entrainment to the day and night by the central biological clock.
6. Possible indications of a lower functioning of photosensitive retinal cells that are key for optimal entrainment of the circadian rhythm to the natural day and night cycle 7. Indications of an effect of light therapy both on a phase advance of the circadian rhythm and on the symptoms of ADHD.
7. The central role of dopamine in ADHD, sleep, and retinal circadian alignment.
8. First indications of the short- and long-term effects of sleep improvement (by sleep hygiene measures, melatonin, light therapy, and SMR neurofeedback in delayed sleep; adenotonsillectomy in sleep apnea, and drug treatment in restless legs syndrome) on the reduction of the severity of ADHD symptoms.

Finally, we propose some scientific direction for future studies:

1. The longitudinal relationship between sleep and ADHD over the lifespan.
2. The functioning of the retinal photosensitive cells of ADHD patients.
3. The additive effect of chronotherapy for the delayed sleep phase disorder to an existing ADHD treatment regime.
4. The effect of treatments for other sleep disorders on ADHD symptomatology.

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**Author's contribution** All authors have contributed to the manuscript and approved the final version.

## Compliance with ethical standards

**Conflict of interest** MA reports options from Brain Resource (Sydney, Australia), is director and owner of Research Institute Brainclinics, a minority shareholder in neuroCare Group (Munich, Germany), and a co-inventor on 4 patent applications (A61B5/0402; US2007/0299323, A1; WO2010/139361 A1; WO2017/099603 A1) related to EEG, neuromodulation, and psychophysiology, but does not own these nor receives any proceeds related to these patents; Research Institute Brainclinics received research funding from Brain Resource (Sydney, Australia) and neuroCare Group (Munich, Germany), and equipment support from Deymed, neuroConn, and Magventure; however, data analyses and writing of this manuscript were unconstrained. The other authors report no conflicts of interest.

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