The Role of the Circadian System in Attention Deficit Hyperactivity Disorder

7

Upasana Bondopadhyay, Unai Diaz-Orueta, and Andrew N. Coogan

Abstract

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental condition characterised by the core symptoms of inattention, impulsivity and hyperactivity. Similar to many other neuropsychiatric conditions, ADHD is associated with very high levels of sleep disturbance. However, it is not clear whether such sleep disturbances are precursors to, or symptoms of, ADHD. Neither is it clear through which mechanisms sleep and ADHD are linked. One possible link is via modulation of circadian rhythms. In this chapter we overview the evidence that ADHD is associated with alterations in circadian processes, manifesting as later chronotype and delayed sleep phase in ADHD, and examine some mechanisms that may lead to such changes. We also interrogate how the circadian clock may be a substrate for therapeutic intervention in ADHD (chronotherapy) and highlight important new questions to be addressed to move the field forward.

Keywords

ADHD · Circadian · Sleep · Attention · Impulsivity

7.1 Clinical Vignette

Frank is a cheerful 9-year-old boy, currently enrolled in primary school, who seems to be imaginative and humorous. In a consultation with a psychologist, his parents reported being concerned about their son's academic performance and certain aspects of his behaviour. As conveyed by his school teachers, staff and by his mother, Frank exhibits certain disruptive behaviours within the classroom/the school premises and sometimes in social gatherings. These behaviours are not resultant from any apparent emotional concerns such as anger, but are for the most times playfully or accidentally occurring due to lack of control in Frank over his own reactions. He also has difficulty sitting still in the class or paying attention during lessons and has a tendency to move around and experiences some difficulties with interpersonal relationships among his peers. Further, Frank has been facing some academic concerns in certain subjects, especially English and Maths. Following careful psychological assessment, it is apparent that Frank possesses an average intellectual ability with a below average academic functioning

Disclosures: The authors have no potential conflicts of interest to disclose.

U. Bondopadhyay · U. Diaz-Orueta · A. N. Coogan (✉)
Department of Psychology, Maynooth University, National University of Ireland, Maynooth, County Kildare, Ireland
e-mail: andrew.coogan@mu.ie

O. Engmann, M. Brancaccio (eds.), *Circadian Clock in Brain Health and Disease*, Advances in Experimental Medicine and Biology 1344, https://doi.org/10.1007/978-3-030-81147-1_7

level in the domain of Mathematics, coupled with clinically significant difficulty in paying selective attention and lack of age appropriate behavioural inhibition, that are leading to substantial levels of concerns in his school performance and functioning in social environments. Frank fulfils the criteria to warrant a diagnosis of attention deficit hyperactivity disorder (ADHD).

Although Frank's primary difficulties were directly related to inattention and difficulty controlling his impulses, upon careful evaluation of his functioning a majority of his disturbances could be interlinked to his day to day functioning and especially to his sleep. Detailed clinical interview revealed that at home Frank would generally start doing his homework late after dinner and would consistently refuse to go to bed at the parentally-designated time; this refusal had led his parents to design most of the work at home towards the later part of the night. Frank generally goes to bed around midnight on school-days and is woken (with difficulty) at 7 am in the morning to leave for school. Most days, in the morning Frank misses his breakfast and forgets to bring his schoolbooks. At school he generally gives the reason that he was asking a classmate for a text/note book during a lesson, when he is found chatting with others and moving around in the class. By break time, Frank partially finishes his lunch to join his friends for free-play. By the later part of the afternoon, teachers report Frank seems irritable and sleepy. On a near daily basis Frank ends up in a physical fight with the student standing in front or behind him in the school yard line. This picture demonstrates how clinically significant inattention and hyperactivity impact on Frank's day-to-day functioning and associate with particular temporal patterns in his psychological and physiological functioning. Frank's presentation is typical for many children with a diagnosis of ADHD and illustrates how the circadian system has a crucial involvement in forming daily patterns of behaviour that manifest as the clinical presentation of ADHD symptoms. This chapter attempts to elucidate the various alterations in the physiological, endocrinological, behavioural and cognitive functioning observed in ADHD that represents disruption in the individual's circadian systems.

7.2 Neuropsychological Presentation of Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which usually emerges in childhood and continues through adulthood in 30–50% of cases (Noggle et al. 2012). ADHD is characterised by the core psychopathological features of inattention, impulsivity and hyperactivity and may be associated with detrimental consequences for the individual as well as for the community as a whole (McGough 2014). ADHD is associated with impairment across various spheres of functioning, including academic achievement, age appropriate interpersonal/social skills, personal health/safety, parenting and occupational outcome (Noggle et al. 2012). According to the DSM-V (APA 2013), ADHD is characterised by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, for at least 6 months to a degree that is inconsistent with the developmental level and that negatively impacts directly on social and academic/occupational activities (5th ed.; DSM–5; American Psychiatric Association 2013) (Table 7.1).

In addition, the diagnostic criteria state that the presence of the above symptoms (as per criteria) should be demonstrated prior to age 12 years and that the symptoms should occur in two or more settings (at home, school or work; with friends or relatives or during other activities). Lastly, symptoms should not occur exclusively during the course of a psychotic disorder and cannot be better explained by another mental disorder (APA 2013).

7.3 ADHD Aetiology

Attention deficit hyperactivity disorder (ADHD) has been a subject of investigation since the

Table 7.1 In the clinical presentation of ADHD in children and adolescents, the presence of either/both the following symptoms (6 or more in each category) represents the diagnostic Criteria (APA 2013)

Symptoms	Inattention	Hyperactivity
A.	Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate)	Often fidgets with or taps hands or feet or squirms in seat
B.	Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading)	Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place)
C.	Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction)	Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless.)
D.	Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily side-tracked)	Often unable to play or engage in leisure activities quietly
E.	Often has difficulty organising tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganised work; has poor time management; fails to meet deadlines)	Is often 'on the go', acting as if 'driven by a motor' (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with)
F.	Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers)	Often talks excessively
G.	Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, and mobile telephones)	Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation)
H.	Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts)	Often has difficulty waiting his or her turn (e.g., while waiting in line)
I.	Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments)	Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing)

beginning of the twentieth century, when Still (1902) described an 11-year-old hyperactive boy who displayed 'loss of moral control' and 'psychical disturbance'. A detailed description of symptoms including hyperkinetic behaviour and loss of motor inhibition was included in his lecture. The core symptoms characterising ADHD (inattention, hyperactivity and impulsivity) have been presented in research and clinical practice guidelines (such as ICD-10 and DSM-V) with relative consistency, with only minor alterations in recent editions of contemporary guidelines. However, the search of insight into the aetiology of ADHD has seen plenty of turns and novel outlooks over the past number of decades. Mattes in 1980s argued that the dysfunctions in the frontal lobe regions are related to ADHD, and Niedermeyer and Naidu (1997) further validated that disinhibition of motor activity and features of inattention observed in ADHD resulted from a 'lazy' rather than a damaged frontal lobe. ADHD symptomatology has strongly pointed towards a lack of executive control. Executive dysfunction in the ADHD clinical picture is

most clearly manifested among other deficits, in the form of a lack of inhibitory control. Inhibitory control can be described as processes that affect information selection at the time of attentional processing and choosing between conflicting situations (or actions) that require the individual to suppress less dominant incongruent information (Bob and Konicarova 2018). For example, in a neuropsychological test (NEPSY-II) of inhibitory control the child must suppress the urge to consider saying the actual colour of the target shape, rather than the test trial rule, where they must say the opposite colour (black for white or white for black). Further studies have shown that ADHD features are mainly concerned with two types of deficits in executive control, the cognitive deficits, related to the attentional concerns and the affective deficits, related to altered emotional reactions. Here the role of an excitable limbic system has been postulated (Antonini et al. 2015; Castellanos et al. 2006; Martinez et al. 2016; Toplak et al. 2005). Therefore, ADHD symptoms may be a result of not only the executive function concerns of the frontal cortex, but also disrupted functioning and structural features of the subcortical brain regions such as those of the limbic system.

Another line of investigations has focussed on the role of dysfunctional catecholamine secretion in ADHD. Animal studies have demonstrated abnormality of the dopaminergic (DA) and norepinephrinergic (NE) systems in ADHD. Rodent studies involving the spontaneous hypertensive rat (SHR) showed reduced level of dopamine in the prenatal SHR mid brain regions and heightened dopamine transporter activity in the adult SHR (Leo et al. 2003; Russell 2007; Watanabe et al. 1997). These studies also emphasise on whether ADHD pathophysiology is a result of a hyperdopaminergic or a hypodopaminergic tendency. In 2003, Viggiano and his colleagues demonstrated low motor activity in gene-knockout model mice that lacked the DA transporter, tyrosine hydroxylase. These mice were observed to be more hyperactive in novel situations and appeared less active on administration of stimulants. This study inclines towards the hyperdopaminergic model of ADHD. The same authors also studying the Naples high excitability (NHE) rat (showing signs of hyperactivity and poor working memory) found increased staining of the DA transporter in the prefrontal cortex. On the other hand, the SHR model displayed low levels of DA in the ventral tegmental, substantia nigra and the caudate nucleus areas and more release of DA in the prefrontal cortex and nucleus accumbens (Adriani et al. 2003). In addition to an inclination towards hypo DA hypothesis, this study suggested the possibility of an impaired DA storage function implicated in ADHD.

Such hypotheses spurred the investigation of neuronal and brain substrates of ADHD through neuroimaging and cognitive neuroscience paradigms. Recent meta-analysis of nearly two decades of work in the cognitive neuroscience of ADHD has revealed that ADHD is associated with executive function domain-specific alterations in a number of brain networks, including impaired deactivation of the default mode network (Rubia 2018). Another important area of investigation has been in the genetics of ADHD; similar to other neurodevelopmental disorders, ADHD is highly heritable (~75%; Faraone and Larsson 2018). A recent genome-wide meta-analysis of ADHD revealed for the first time 12 loci associated with ADHD that are statistically significant at the genome-wide level (Demontis et al. 2019). Although the level of variance explained by these individual genetic associations remains very modest, these recent findings do support the hypothesis that ADHD symptoms represent extremes of heritable traits expressed in the general population. Unfortunately, both cognitive neuroscience and genetic studies of ADHD have yet to be translated into widespread clinical practice, although there are some promising areas with an accumulating evidence base (e.g., neurofeedback; Enriquez-Geppert et al. 2019).

7.4 Sleep in ADHD

Children diagnosed with ADHD often have disturbed lifestyles, with a host of disorganised behaviours constantly tinting their daily lives.

Although these behaviours may be goal directed, they frequently end up being incomplete or filled with errors, resulting in detrimental implications for their mental health and occupational endeavours. Within the facets of their disturbed lifestyle, individuals with ADHD often report experiencing sleep related concerns and disturbances in considerable excess compared to matched control groups (Owens 2009). Co-occurrence of sleep concerns and ADHD reflect their prevalence in a pronounced way, with 70% of individuals with ADHD having sleep related concerns (Yoon et al. 2012) as opposed to 20–30% in the general population (Quach et al. 2012). Such sleep related concerns reported include sleep onset problems manifesting in long sleep latency, sleep phase delay syndrome, increased periodic limb movements during sleep, daytime sleepiness and altered total sleep (Corkum et al. 1998; Cortese et al. 2006; Konofal et al. 2001, 2010; Mayes et al. 2009). A number of the above concerns are expressed as difficulty in initiating and maintaining sleep (Ball et al. 1997) and the severity of sleep problems may be associated with the severity of ADHD symptoms and may be useful therapeutic targets for ADHD symptom management (Sciberras et al. 2019). Further, in the general population sleep disturbances may be associated with inattention and hyperactivity; for example, Sung et al. (2008) demonstrated that children with behavioural sleep problems also experienced more ADHD-like symptoms, lower quality of life and daily functioning. As such, dysfunctional behavioural traits associated with ADHD might be related to impaired sleep functioning, which in turn acts as a maintaining factor for the condition, fuelling the core characteristic features of the disorder (Coogan et al. 2016a). Indeed, some authors have recently questioned whether ADHD should be considered primarily as a sleep disorder (Bijlenga et al. 2019). However, there are a number of central questions that remain unanswered in relation to the sleep-ADHD associations, including questions of causality, directionality and mechanism (Raman and Coogan 2019).

7.5 The Circadian System and ADHD

Both objective and subjective assessment tools examining the rest and activity cycles among individuals with ADHD (children, adolescents and adults) have shown significant variations in daily rhythms in a number of behavioural, cognitive, endocrine, physiological and molecular parameters when compared to typically functioning individuals (Korman et al. 2019). An important behavioural and psychological manifestation of variations in circadian functioning is chronotype/diurnal preference (Adan et al. 2012). Chronotype/diurnal preference can be broadly conceptualised as inter-individual differences in actual or preferred timing of sleep/wake behaviours, and psychometric and other instruments such as Morningness/Eveningness Questionnaire (Horne and Ostberg 1976), Composite Scale of Morningness (CSM, Smith et al. 1989) and Munich ChronoType Questionnaire (MCTQ, Roenneberg et al. 2003) can be used for its assessment. Both children and adults with ADHD have been found to have a significant preference for eveningness/later chronotype, characterised as later bedtime and wake time or an increased psychological preference for such later timings of sleep behaviours (Baird et al. 2012; Rybak et al. 2007; Voinescu et al. 2012). In a systematic review (Coogan and McGowan 2017), nine target studies were found to demonstrate diurnal preferences among ADHD samples. In a 2007 study, Rybak and his colleagues showed an association between eveningness and ADHD symptoms such as poorer sustained attention among 29 diagnosed adults. More recently, Durmus et al. (2017) found significantly greater eveningness preference among 7–12-year-old children mostly with ADHD-Combined type, when compared to the control group. Further in this study a positive correlation was found between the eveningness scores and total score on resistance to sleep time. Gamble et al. (2013) reported a positive correlation between delay in rest/activity cycle and the severity of ADHD symptoms among adults. Rybak et al. (2007)

also documented a correlation between greater eveningness with increased inattention and impulsivity. These findings point towards a direct relationship between chronotype preferences and major ADHD characteristics.

Examining rhythms of sleep/wake behaviours in non-clinical samples aids in delineating which ADHD symptoms may be associated with later chronotype/evening preference. For example, McGowan in 2016 demonstrated among 396 adults that the construct of Social Jetlag (the mismatch of the time of midsleep on work versus 'free' days indicative of tension between circadian and behavioural cycles), rather than chronotype is a predictor of ADHD symptom of impulsivity. Similar association has also been demonstrated through negative correlations between scores on 'morningness' and symptoms of inattention when using subjective questionnaires (Caci et al. 2009). Later chronotype is associated with greater social jetlag (e.g., Roenneberg et al. 2012), and as such it may be that social jetlag, and not chronotype per se, is the factor associated with impulsivity and other ADHD symptoms. Other studies have linked later and more variable sleep timing with trait impulsivity (McGowan and Coogan 2018), and have also linked later chronotype with other behavioural manifestations of impulsivity, including sensation seeking and response inhibition (Kang et al. 2015). Ottoni et al. (2012) report that eveningness is associated with being emotionally volatile and the behavioural traits of ADHD such as apathetic and disinhibited temperamental inclinations. Therefore, there may be widespread influence of the circadian system on the individual's cognitive, affective, behavioural domains that are pertinent for ADHD symptomatology.

As illustrated in the clinical vignette case of Frank, his behavioural symptoms governing lack of inhibitory control revealed through psychological test findings as well as subjective reports are related perhaps to his altered sleep timings, which in turn may be the result of inclination towards later chronotype. Therefore, Frank's temperamental reactions with peers or with others in his social environments and his frequent tendency to get into unpleasant physical interactions with peers may in part reflect chronobiological traits.

7.6 Delayed Sleep Phase and Sleep Onset Insomnia in ADHD

Gruber et al. (2000), using both subjective reports of sleep log and objective findings from actigraphic recordings from 7- to 11-year-old children diagnosed with ADHD, demonstrated that ADHD was associated with more variable and later sleep onset time compared to controls. Subsequently, similar findings were reported both for younger children and older adolescents (Hvolby et al. 2008; Hysing et al. 2016). Van der Heijden et al. (2005) reported that the presence of sleep onset insomnia in children with ADHD is associated with significantly longer sleep latencies and delayed dim-light melatonin onset (DLMO) compared to children with ADHD but no sleep onset insomnia. Bron et al. (2016) found that adults with lifetime depression/anxiety (LDA) in addition to high ADHD symptoms were found to have the least favourable sleep characteristics as compared to the individuals in the depression/anxiety and control group, and that the LDA and ADHD group were found to have the highest results for Delayed Sleep Phase Syndrome, shortest sleep duration and extremely late chronotype. Van Veen et al. (2010) found that, out of 40 ADHD adults, 31 reported the presence of sleep onset insomnia and were also found to have a delayed DLMO, indicated a significantly delayed phase of circadian entrainment. In a large retrospective cohort of 9338 adolescents, a significant association was found between delayed sleep phase disorder (DSPD) and inattentive and hyperactive symptoms (Sivertsen et al. 2015), indicating potential for delayed sleep phase to feed into ADHD symptoms.

The pineal hormone melatonin's synthesis in the pinealocytes from the precursor tryptophan exhibits a clear circadian rhythm, with peak plasma levels usually between 2 and 3 am, and the master pacemaker in the suprachiasmatic nucleus (SCN, located in the anterior ventral

hypothalamus) has indirect efferent projections to the pineal gland crucial for synchronising the circadian rhythm of melatonin to the light-dark cycle and maintaining its persistence (Arendt 2005a). As such, delays in DLMO observed in ADHD may be indicative of altered entrainment of the SCN master clock to environmental zeitgebers. However, to date there has been no direct examination of SCN function in ADHD (for example, in post mortem tissue), and other work to date has focussed on the use of peripheral (and accessible) circadian oscillators as proxies for circadian function in ADHD (e.g., Baird et al. 2012; Coogan et al. 2019).

Psychopharmacological factors might also influence the presence of longer sleep latency and other insomnia symptoms sleep in ADHD. In a study by Boonstra et al. (2007), administration of methylphenidate (MPH, the frontline psychostimulant used in the pharmacological management of ADHD) in adults diagnosed with ADHD has been linked to anomalies in sleep parameters, such as concerns with sleep latency and sleep duration. However, the same study also documented evidence of lesser nocturnal awakenings and hence a more consolidated sleep because of MPH (Boonstra et al. 2007). Among the younger ADHD populations, methylphenidate has been linked to a shorter total sleep time and later sleep onset times in several investigations (Lee et al. 2012; Sangal et al. 2006; Snitselaar et al. 2013; Tirosh et al. 1993). Another recent study demonstrated that pharmacotherapy of ADHD was associated with alterations in circadian and sleep function in adults with ADHD when compared to treatment-naïve ADHD patients (Coogan et al. 2019). For example, treatment was associated with longer, but not more frequent, wake bouts during the night in medicated patients. As such, it is important to delineate the associations of ADHD itself with sleep and circadian changes from ADHD-treatment effects.

Returning to the case of Frank, his consistently later bedtimes (and the resultant short sleep duration, as he wakes up by 7 am) could be attributed to the possible presence of a delayed sleep phase (although no sleep measures were used in his assessment particularly). This delayed sleep phase may be directly amplifying Frank's manifestation of inattention or hyperactivity. Alternatively, or additionally, shortened sleep duration may be important as this has been associated with hyperactivity and inattention in a study with a large adolescent cohort (Gau et al. 2007). Therefore, functionally, later bedtimes could be a crucial influencing factor for Frank's ADHD symptoms.

7.7 Genetic and Environmental Factors That May Link ADHD and the Circadian System

As mentioned earlier, ADHD is a highly heritable disorder. Circadian traits are also reported to be heritable; for example, chronotype appears to be strongly heritable (Inderkum and Tarokh 2018) and genome-wide studies have revealed significant associations with polymorphisms in clock genes and other loci (e.g., Jones and Jane 2019). As such, there is the possibility for shared genetic risk between ADHD and circadian traits associated with ADHD. Although at present no association between ADHD and clock genes has been reported at the genome-wide level, there are some interesting reports from candidate gene studies (notwithstanding the recognised weaknesses of such approaches; Duncan et al. 2019). *PER1* has been associated with ADHD in children and adolescents (Lasky-Su et al. 2008) and *PER2* polymorphisms has also been associated with ADHD (Brookes et al. 2006), although these associations did not reach genome-wide statistical significance. A single nucleotide polymorphism in the CLOCK gene has been associated with adult ADHD symptoms in three separate studies (Jeong et al. 2014; Kissling et al. 2008; Xu et al. 2010). In a recent study, Carpena et al. (2019) explored the association between ADHD and *CLOCK*, using haplotype analysis, and demonstrated an association between *CLOCK* haplotype and ADHD status, further implicating *CLOCK* in the aetiology of ADHD. There have also been a number of studies that examined the diurnal rhythms in expression

of clock genes in different tissues derived from ADHD patients. Baird et al. (2012) reported that, in adults, ADHD is associated with blunting of rhythms in the expression profiles of the clock genes *BMAL1* and *PER2*. Coogan et al. (2019) also reported ADHD-related changes in clock gene expression profiles in ex-vivo cultures of fibroblasts derived from patients with ADHD (and with or without ADHD medication). These data indicate that there may be alterations in the core molecular circadian cycle associated with ADHD, and warrants further study.

As light is the most important environmental zeitgeber that determines circadian phase, it is possible that geographical variations in the timing and levels of exposure to sunlight might influence ADHD prevalence. Arns et al. (2013) tested this hypothesis when they analysed the record of solar intensity from ten countries, reporting associations between higher solar intensities and lower ADHD prevalence. The proposed mechanism that may underpin this association is that bright morning light would phase advance the circadian clock and decrease the association between delayed phase and ADHD symptoms. In 2015, Huber and his co-workers stated that higher altitude geographical regions have lower prevalence of ADHD, based their rationale on the association of higher altitude with hypobaric hypoxia and hence increased levels of dopamine. Based on the hypodopaminergic model of ADHD, such an increase in the dopamine would mitigate against ADHD. However, Arns et al. (2015) found that the association of altitude with ADHD prevalence is actually related to the solar intensity levels rather than the altitude level, which must have been the confounding factor detected previously. The influence of natural sunlight, mediated through the biological clock, on ADHD symptoms may offer therapeutic opportunities through increasing exposure to daylight.

7.8 Neuroendocrine and Autonomic Features of ADHD: Circadian Aspects

Turner-Cobb (2005) showed that the hypothalamus pituitary adrenal (HPA) axis plays an important role in regulating neurobehavioural domains such as attention, emotion, learning, memory and movement. Under a stressful condition, the neurons of the hypothalamus release the corticotropic hormone which in turn leads to the secretion of the adrenocorticotropic hormone and the subsequent secretion and release of cortisol from the adrenal cortex. In a study by Musser in 2011 it was found that there were no significant sympathetic variations found in ADHD children when they were shown emotional stimuli as opposed to typically functioning individuals, supporting the hypothesis of autonomic dysregulation in individuals with ADHD. This under-reactivity of the HPA was also found to correlate with the neurocognitive performance of the ADHD individual and was further demonstrated empirically by measuring low levels of cortisol for ADHD patients as compared to the control group in a study by Ma and colleagues in 2011. Abnormal diurnal cortisol rhythms have been linked with hyperactivity manifested in childhood features of ADHD (Blomqvist et al. 2007; Kaneko et al. 1993) and this finding is crucial as the HPA axis is under strong circadian control (Nicolaides et al. 2014). Further, the diurnal profile of cortisol expressed relative to habitual wake time appears to be phase-delayed in adults with ADHD compared to controls (Baird et al. 2012), whilst children with ADHD show morning hypo-arousal of the HPA axis as assessed via salivary cortisol levels (Imeraj et al. 2012). Dysfunction in arousal mechanisms can be viewed as the causal factor for ADHD, with motor hyperactivity being considered a reaction to the hypo-arousal condition that is required to counteract somnolence (Lecendreux et al. 2000). Hence, hypo-reactivity of the HPA axis in stressful condition has been linked to the symptoms of hyperactivity and impulsivity in ADHD (Blomqvist et al. 2007; Hong et al. 2003; Moss et al. 1995; Virkkunen

1985). This behavioural hyperactivity and impulsiveness is expressed in the form of a significant lack of behavioural inhibition characterising their psychosocial reactions. Hong et al. (2003) postulated therefore that an abnormal HPA-axis response to stress should be considered as an attributional factor for the dysfunctional behavioural inhibition observed in ADHD. A corollary of this hypothesis is that given the HPA operates under strong circadian influence, that dysfunction of HPA function in ADHD may be associated with altered rhythms in HPA processes.

The possible dysfunction of the HPA axis has been linked to the major defining characteristics found in ADHD which are cognitive, affective and behavioural in nature. Lack of behavioural inhibition has been linked to the problematic behaviours observed in ADHD (Lackschewitz et al. 2008), and such impairing behaviours should be considered in line with the abnormal HPA-axis response to stress (Hong et al. 2003). Low levels of cortisol has been associated with lack of age appropriate cognitive performance (Hong et al. 2003), maladaptive behaviours as well as variations in levels of anxiety among ADHD children (Hastings et al. 2009); these findings have also been replicated in adults with ADHD (Lackschewitz et al. 2008). Certain studies have shed light upon specific relationship between the ADHD subtype and under-reactivity of HPA axis in response to stress. Both hyperactivity/impulsive subtype and the inattentive subtype have been linked to dysfunctional HPA activation (Hong et al. 2003; Moss et al. 1995; Randazzo et al. 2008; Virkkunen 1985). However these findings are not completely consistent; for example, Van West et al. (2009) did not find a relation between low cortisol responsivity and psychosocial stress. These discrepancies however could be attributed to the study sample, design, comorbidity or treatment effects.

7.9 Chronotherapy for ADHD

If circadian rhythms are indeed altered in ADHD, and these alterations are linked to specific features of the condition, then interventions to re-synchronise the circadian cycles might then be particularly effective in alleviating these symptoms. A number of studies have examined the effect of melatonin treatment on ADHD symptoms and sleep related outcomes. The nature of the current evidence base for the utility of melatonin in ADHD management include randomised, placebo controlled and double-blind trials to longitudinal investigations on samples of ADHD or typically developing individuals (Coogan and McGowan 2017). Systematic administration of melatonin has been associated with significant decrease in sleep onset latency and increase in sleep duration among the participants. For example, in a recent study by Masi et al. (2019), ADHD children and adolescents treated with methylphenidate were administered melatonin for a period of 1–12 months, and both younger children and adolescents reported improvements in sleep concerns. Other studies over the past decade have been more specific with regard to sleep outcomes as a result of melatonin use. Tjon Pian Gi et al. (2003) reported a rapid decrease in sleep onset latency upon prior to bedtime administration of melatonin among children with ADHD and insomnia. Another earlier study even reported a decrease of sleep onset latency from 60 to 30 min as a result of melatonin treatment for 4 weeks (Smits et al. 2001). Different studies have also argued regarding the best possible design and co-treatment that might lead to best sleep related outcome among the patients. Weiss et al. (2006) demonstrated that maximum reduction in insomnia symptoms took place when melatonin administration was coupled with sleep hygiene training. Similarly a decrease in sleep latency resulted from the co-administration of melatonin with methylphenidate, accompanied by an increase in the height and weight of the participating children (Mostafavi et al. 2012). Further, another study following a similar design of co-administering melatonin and methylphenidate showed decrease in sleep onset latency, but did not result in improvements of core ADHD symptoms (Mohammadi et al. 2012). Therefore, the above studies point towards the positive

effects of melatonin in improving sleep onset among ADHD; however, the treatment has not shown direct effect on the symptoms of inattention or hyperactivity/impulsivity.

With regard to delayed sleep phase, melatonin administration has shown some positive effects. A meta-analysis (Van Geijlswijk et al. 2010) reported that exogenous intake of melatonin leads to the advancement of the endogenous melatonin onset in both children and adolescents. In 2006, Szeinburg showed that a 6 months intake of melatonin resulted in shorter sleep latency and longer sleep duration among a group of children and adolescents diagnosed with delayed sleep phase syndrome. Melatonin treatment has shown advancement of DLMO, indicating melatonin's utility in correcting delayed circadian phase (Van der Heijden et al. 2007). One question of importance regarding melatonin in these studies is whether melatonin is deployed primarily as a somnolent or as a chronobiotic; the doses and timing of optimal treatments will differ accordingly, and as such this clear distinction should be made at the conception of studies (Arendt 2005b).

Behavioural chronotherapeutic interventions for treatment of circadian and/or sleep related concerns in ADHD populations over the last decade have shown some promise. Mullane and Corkum (2006) investigated the effect of behavioural intervention for sleep in three unmedicated children over a 5-week treatment period and found that the children's sleep improved and were maintained over a 3-month follow-up period. Corkum et al. (2009) validated the above findings on a larger randomised control trial (RCT), where the ADHD children were found to have significantly improved sleep as compared to typically functioning control group. The intervention included facets such as psychoeducation about basic sleep physiology and the different types of sleep problems/disorders, sleep hygiene and bedtime routines, implementing a faded bedtime strategy and reward program (Mullane and Corkum 2006). Over the following period other well-designed RCTs also supported the effectiveness of behavioural interventions for the improvement of sleep concerns in ADHD sample of participants (Hiskock et al. 2015; Keshavarzi et al. 2014). Hiskock et al. (2015) found significantly improved ADHD symptoms (through parent and teacher ADHD rating scale), sleep problems (parent reported severity through children's sleep habits questionnaire and actigraphy), behaviour and daily functioning (measured through strengths and difficulties questionnaire) and working memory (working memory test battery for children) because of the behavioural sleep intervention-controlled trial. Similar results were also highlighted by Peppers et al. (2016) where sleep hygiene program led to better sleep quality and improved ADHD symptoms.

The use of morning bright light therapy among ADHD children has been shown to result in correction of delayed sleep phase and also improvements in ADHD ratings (Gruber et al. 2007). Similar findings (alleviation of core ADHD symptoms and improvements in affective symptoms) have also been demonstrated in case of adults that demonstrated that shifts towards earlier circadian preference were associated with improvement in the overall subjective and objective ADHD symptom ratings (Rybak et al. 2006). Other preliminary pilot findings further support the principle that light therapy as a chronotherapeutic may be useful in the management of ADHD symptoms: Fargason et al. (2017) report that morning bright light, coupled with the minimisation of evening bright light, advanced DLMO and was associated with decreased ADHD scores. Given the promise of light therapy in other areas of psychiatry and psychology (Cunningham et al. 2019), further study of this strategy in ADHD is warranted.

Agomelatine is a licenced antidepressant in the European Union and Australia, which is an agonist of MT1 and MT2 melatonin receptor and an antagonist of 5-HT2c and 5-HT2B serotonin receptors that at least partially functions as a chronobiotic (Guardiola-Lemaitre et al. 2014). Preliminary evidence has suggested that agomelatine treatments lead to decreased ADHD-related symptoms (Niederhofer 2012). Salardini et al. (2016) reported in a study with a

small group of ADHD children and adolescents that outcomes related to ADHD symptoms were not significantly better for the agomelatine-treated group than those treated with methylphenidate; however, the former reported less concerns associated with insomnia as a treatment outcome. Although these findings reveal some promise, concerns around hepatotoxicity with agomelatine and the lack of licensing in major jurisdictions are likely to curtail interest in further exploring its use in ADHD, and future studies may rather focus on other melatoninergic agonists (Comai et al. 2019).

In the clinical vignette case of Frank, his habitually late bedtime could be reinforcing a delayed circadian and sleep phase through increased exposure to evening light, which will delay the circadian clock (Raman and Coogan 2019). As such, there is potential for a 'vicious cycle' to develop, though which late bedtime reinforces late bedtime. Equally however, there may be an opportunity here to break this cycle through increasing morning light exposure (coupled with decreased evening light exposure), phase advancing the clock and helping establish more socially-congruent sleep/wake behavioural cycles. The utility of such approaches may vary strongly between individuals, as recent evidence indicates very high levels of inter-individual variability in responses to light (Phillips et al. 2019).

7.10 Future Directions

The current literature leaves a number of important questions still unanswered in relation to ADHD and altered circadian rhythms. Chief amongst these is whether circadian changes are symptoms of ADHD, or precursors to ADHD, or risk factors for ADHD, or a mix of these? There are some suggestions from recent longitudinal studies that suggest sleep disturbances preface and predict ADHD diagnosis in young children (Soehner et al. 2019; Tso et al. 2019). Indeed, there have been recent suggestions that ADHD might be reasonably reconceptualised as a sleep disorder, with ADHD features emerging (in part) as a neurocognitive result of chronic sleep disturbances and circadian changes (Bijlenga et al. 2019).

Certainly, it would appear that cognitive and behavioural strategies to improve sleep and/or circadian function in ADHD might be expected to yield benefit. Inspiration for those of us working in the field of ADHD comes from findings in major depression that indicated that Cognitive Behavioural Therapy for insomnia (CBTi) results in significant and durable antidepressant effects (e.g., Kalmbach et al. 2019). Indeed, large trials of internet-delivered interventions indicate that CBTi results in improvements in psychopathology and quality of life (Espie et al. 2019). Thus, trials of CBTi in ADHD appear to be strongly warranted. Chronotherapy incorporating bright light therapy may also be a useful treatment modality and has shown much promise in other diagnoses (Cunningham et al. 2019). Further, circadian principles may be deployed in the pharmacotherapy of ADHD: either through the use of melatonin or melatoninergic agonists as chronobiotics, or through the use of circadian medicine to identify time-of-day for optimal effectiveness of psychostimulants used routinely in the treatment of ADHD (Ruben et al. 2019).

Incorporating perspectives from chronobiology into ADHD research and practice may lead to advances in our understanding of ADHD, and improvements in the lives of patients like Frank, as well as their families and carers.

References

Adan A, Archer SN, Hidalgo MP et al (2012) Circadian typology: a comprehensive review. Chronobiol Int 29 (9):1153–1175

Adriani W, Caprioli A, Granstrem O et al (2003) The spontaneously hypertensive-rat as an animal model of ADHD: evidence for impulsive and non-impulsive subpopulations. Neurosci Biobehav Rev 27:639–651

American Psychiatric Association (2013) Neurodevelopmental disorders. In Diagnostic and statistical manual of mental disorders (5th ed.). https://doi.org/10.1176/appi.books.9780890425596.dsm01

Antonini TN, Becker SP, Tamm L, Epstein JN (2015) Hot and cool executive functions in children with attention-deficit/hyperactivity disorder and comorbid

oppositional defiant disorder. J Int Neuropsychol Soc 21(8):584–595
Arendt J (2005a) Melatonin in humans: it's about time. J Neuroendocrinol 17:537–538
Arendt J (2005b) Melatonin: characteristics, concerns, and prospects. J Biol Rhythm 20:291–303
Arns M, van der Heijden KB, Arnold LE, Kenemans JL (2013) Geographic variation in the prevalence of attention-deficit/hyperactivity disorder: the sunny perspective. Biol Psychiatry 74:585–590
Arns M, Swanson JM, Arnold LE (2015) ADHD prevalence: altitude or sunlight? Better understanding the interrelations of dopamine and the circadian system. J Atten Disord 22(2):163–166
Baird AL, Coogan AN, Siddiqui A, Donev RM, Thome J (2012) Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural endocrine and molecular levels. Mol Psychiatry 17(10):988–995
Ball J, Tiernan M, Janusz J, Furr A (1997) Sleep patterns among children with attention-deficit hyperactivity disorder: a reexamination of parent perceptions. J Pediatr Psychol 22:389–398
Bijlenga D, Vollebregt MA, Kooij JJS, Arns M (2019) The role of the circadian system in the etiology and pathophysiology of ADHD: time to redefine ADHD? Atten Defic Hyperact Disord 11(1):5–19
Blomqvist M, Holmberg K, Lindblad F, Fernell E, Ek U, Dahllöf G (2007) Salivary cortisol levels and dental anxiety in children with attention deficit hyperactivity disorder. Eur J Oral Sci 115:1–6
Bob P, Konicarova J (2018) ADHD, stress, and development. Springer, Cham
Boonstra AM, Kooij JJ, Oosterlaan J, Sergeant JA, Buitelaar JK, Van Someren EJ (2007) Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. Sleep 30:433–442
Bron T, Bijlenga D, Kooij JJ et al (2016) Attention-deficit hyperactivity disorder symptoms add risk to circadian rhythm sleep problems in depression and anxiety. J Affect Disord 200:74–81
Brookes K, Chen XXW, Zhou K et al (2006) The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in DRD4, DAT1 and 16 other genes. Mol Psychiatry 11:53–934
Caci H, Bouchez J, Bayle FJ (2009) Inattentive symptoms of ADHD are related to evening orientation. J Atten Disord 13:36–41
Carpena MX, Hutz MH, Salatino-Oliveira A et al (2019) CLOCK polymorphisms in attention-deficit/hyperactivity disorder (ADHD): further evidence linking sleep and circadian disturbances and ADHD. Genes (Basel) 10(2):E88
Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R (2006) Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci 10:117–123
Comai S, Bertazzo A, Vachon J et al (2019) Trace elements among a sample of prisoners with mental and personality disorders and aggression: correlation with impulsivity and ADHD indices. J Trace Elem Med Biol 51:123–129
Coogan AN, McGowan NM (2017) A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. Atten Defic Hyperact Disord 9:129–147
Coogan AN, Baird AL, Popa-Wagner A, Thome J (2016a) Circadian rhythms and attention deficit hyperactivity disorder: the what, the when and the why. Prog Neuropsychopharmacol Biol Psychiatry 67:74–81
Coogan AN, Schenk M, Palm D et al (2019) Impact of adult attention deficit hyperactivity disorder and medication status on sleep/wake behavior and molecular circadian rhythms. Neuropsychopharmacol 44:1198–1206
Corkum P, Tannock R, Moldofsky H (1998) Sleep disturbance in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 37:637–646
Corkum P, Davidson F, Lingley-Pottie P et al (2009) Behavioral treatment for diagnosed pediatric insomnia in school-aged children. In: Fifth annual conference on pediatric sleep medicine (symposium), Denver, CO
Cortese S, Konofal E, Yareman N, Mouren MC, Lecendreux M (2006) Sleep and alertness in children with attention deficit/hyperactivity disorder: a systematic review of the literature. Sleep 29:504–511
Cunningham JEA, Stamp JA, Shapiro CM (2019) Sleep and major depressive disorder: a review of non-pharmacological chronotherapeutic treatments for unipolar depression. Sleep Med. https://doi.org/10.1016/j.sleep.2019.04.012
Demontis D, Walters RK, Martin J et al (2019) Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 51 (1):63–75
Duncan LE, Ostacher M, Ballon J (2019) How genome-wide association studies (GWAS) made traditional candidate gene studies obsolete. Neuropsychopharmacology 44(9):1518–1523
Durmus FB, Armaan AR, Ayaaz AB (2017) Chronotype and its relationship with sleep disorders in children with attention deficit hyperactivity disorder. Chronobiol Int 34(7):886–894
Enriquez-Geppert S, Smit D, Pimenta MG et al (2019) Neurofeedback as a treatment intervention in ADHD: current evidence and practice. Curr Psychiatry Rep 21:46
Espie CA, Emsley R, Kyle SD et al (2019) Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: a randomized clinical trial. JAMA Psychiatry 76 (1):21–30
Faraone SF, Larsson H (2018) Genetics of attention deficit hyperactivity disorder. Mol Psychiatry 24:562–575
Fargason RE, Fobian AD, Hablitz LM et al (2017) Correcting delayed circadian phase with bright light therapy predicts improvement in ADHD symptoms: a pilot study. J Psychiatr Res 91:105–110

Gamble KL, May RS, Besing RC, Tankersly AP, Fargason RE (2013) Delayed sleep timing and symptoms in adults with attention-deficit/hyperactivity disorder: a controlled actigraphy study. Chronobiol Int 30 (4):598–606

Gau SS, Kessler RC, Tseng WL, Wu YY, Chiu YN, Yeh CB et al (2007) Association between sleep problems and symptoms of attention-deficit/hyperactivity disorder in young adults. Sleep 30:195–201

Gruber R, Sadeh A, Raviv A (2000) Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 39 (4):495–501

Gruber R, Grizenko N, Joober R (2007) Delayed sleep phase syndrome, ADHD, and bright light therapy. J Clin Psychiatry 68(2):337–338

Guardiola-Lemaitre B et al (2014) Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties. Br J Pharmacol 171 (15):3604–3619

Hastings PD, Fortier I, Utendale WT, Simard LR, Robaey P (2009) Adrenocortical functioning in boys with attention-deficit/hyperactivity disorder: examining subtypes of ADHD and associated comorbid conditions. J Abnorm Child Psychol 37(4):565–578

Hiskock H, Sciberras E, Mensah F et al (2015) Impact of a behavioural sleep intervention on symptoms and sleep in children with attention deficit hyperactivity disorder, and parental mental health: randomised controlled trial. BMJ 350(h68):1–14

Hong HJ, Shin DW, Lee EH, Oh YH, Noh KS (2003) Hypothalamic–pituitary–adrenal reactivity in boys with attention deficit hyperactivity disorder. Yonsei Med J 44:608–614

Horne JA, Ostberg O (1976) A self-assessment questionnaire to determine morningness eveningness in human circadian rhythms. Int J Chronobiol 4(2):97–110

Huber RS, Kim TS, Kim N, Kuykendall MD, Sherwood SN, Renshaw PF, Kondo DG (2015) Association between altitude and regional variation of ADHD in youth. J Atten Disord 22(14):1299–1306

Hvolby A, Jørgensen J, Bilenberg N (2008) Actigraphic and parental reports of sleep difficulties in children with attention-deficit/hyperactivity disorder. Arch Pediatr Adolesc Med 162(4):323–329

Hysing M, Lundervold AJ, Posserud MB, Sivertsen B (2016) Association between sleep problems and symptoms of attention deficit hyperactivity disorder in adolescence: results from a large population-based study. Behav Sleep Med 14(5):550–564

Imeraj L, Antrop I, Roeyers H, Deschepper E, Bal S, Deboutte D (2012) Time-of-day effects in arousal: disrupted diurnal cortisol profiles in children with ADHD. J Child Psychol Psychiatry 53(7):782–789

Inderkum AP, Tarokh L (2018) High heritability of adolescent sleep–wake behavior on free, but not school days: a long-term twin study. Sleep 41(3):1–9

Jeong SH, Yu JC, Lee C, Choi KS, Choi JE, Kim SJ, Joo EJ (2014) Human CLOCK gene-associated attention deficit hyperactivity disorder-related features in healthy adults: quantitative association study using Wender Utah Rating Scale. Eur Arch Psychiatry Clin Neurosci 264:71–81

Jones SE, Jane JN (2019) Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms. Nat Commun 10:343

Kalmbach DA, Cheng P, Arnedt T et al (2019) Improving daytime functioning, work performance, and quality of life in postmenopausal women with insomnia: comparing cognitive behavioral therapy for insomnia, sleep restriction therapy, and sleep hygiene education. J Clin Sleep Med 15(7):999–1010

Kaneko M, Hoshino Y, Hashimoto S, Okano T, Kumashiro H (1993) Hypothalamic–pituitary–adrenal axis function in children with attention-deficit hyperactivity disorder. J Autism Dev Disord 23:59–65

Kang JI, Park CI, Sohn SY, Kim HW, Namkoong K, Kim SJ (2015) Circadian preference and trait impulsivity, sensation-seeking and response inhibition in healthy young adults. Chronobiol Int 32:235–241

Keshavarzi Z, Bajoghli H, Mohamadi MR et al (2014) In a randomized case-control trial with 10-years olds suffering from attention deficit/hyperactivity disorder (ADHD) sleep and psychological functioning improved during a 12-week sleep-training program. World J Biol Psychiatry 15(8):609–619

Kissling C, Retz W, Wiemann S, Coogan AN et al (2008) A polymorphism at the 3′-untranslated region of the CLOCK gene is associated with adult attention-deficit hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 147:333–338

Konofal E, Lecendreux M, Bouvard MP, Mouren-Simeoni M (2001) High levels of nocturnal activity in children with attention-deficit hyperactivity disorder: a video analysis. Psychiatry Clin Neurosci 55:97–103

Konofal E, Lecendreux M, Cortese S (2010) Sleep and ADHD. Sleep med 11(7):652–658

Korman M, Palm D, Uzoni A, Faltraco F, Tucha O, Thome J et al (2019) ADHD 24/7: circadian clock genes, chronotherapy and sleep/wake cycle insufficiencies in ADHD. World J Biol Psychiatry 5:1–16

Lackschewitz H, Hüther G, Kröner-Herwig B (2008) Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). Psychoneuroendocrinology 33:612–624

Lasky-Su J, Neale BM, Franke B et al (2008) Genome-wide association scan of quantitative traits for attention deficit hyperactivity disorder identifies novel associations and confirms candidate gene associations. Am J Med Genet B Neuropsychiatr Genet 147B:1345–1354

Lecendreux M, Konofal E, Bouvard M, Falissard MC et al (2000) Sleep and alertness in children with ADHD. J Child Psychol Psychiatry 41:803–812

Lee SH, Seo WS, Sung HM et al (2012) Effect of methylphenidate on sleep parameters in children with ADHD. Psychiatry Invest 9(4):384–390

Leo D, Sorrentino E, Volpicelli F et al (2003) Altered midbrain dopaminergic neurotransmission during development in an animal model of ADHD. Neurosci Biobehav Rev 27:661–669

Martinez L, Prada E, Satler C, Tavares MC, Tomaz C (2016) Executive dysfunctions: the role in attention deficit hyperactivity and post-traumatic stress neuropsychiatric disorders. Front Psychol 7:1230

Masi G, Fantozzi P, Villafranca A et al (2019) Effects of melatonin in children with attention-deficit/hyperactivity disorder with sleep disorders after methylphenidate treatment. Neuropsychiatr Dis Treat 15:663–667

Mattes JA (1980) The role of frontal lobe dysfunction in childhood hyperkinesis. Compr Psychiatry 21:358–369

Mayes SD, Calhoun SL, Bixler ED et al (2009) ADHD subtypes and comorbid anxiety, depression, andoppositional-defiant disorder: differences in sleep problems. J Pediatr Psychol 34:328–337

McGough J (2014) ADHD: ADHD. Retrieved from https://ebookcentral.proquest.com

McGowan NM, Coogan AN (2018) Sleep and circadian rhythm function and trait impulsivity: an actigraphy study. Psychiatry Res 268:251–256

McGowan NM, Voinescu BI, Coogan AN (2016) Sleep quality, chronotype and social jetlag differentially associate with symptoms of attention deficit hyperactivity disorder in adults. Chronobiol Int 33 (10):1433–1443

Mohammadi MR, Mostafavi SA, Keshavarz SA et al (2012) Melatonin effects in methylphenidate treated children with attention deficit hyperactivity disorder: a randomized double blind clinical trial. Iran J Psychiatry 7(2):87–92

Moss HB, Vanyukov MM, Martin CS (1995) Salivary cortisol responses and the risk for substance abuse in prepubertal boys. Biol Psychiatry 3:547–555

Mostafavi SA, Mohammadi MR, Hosseinzadeh P et al (2012) Dietary intake, growth and development of children with ADHD in a randomized clinical trial of Ritalin and Melatonin co-administration: through circadian cycle modification or appetite enhancement? Iran J Psychiatry 7(3):114–119

Mullane J, Corkum P (2006) Case series: evaluation of a behavioural sleep intervention for three children with attention-deficit/hyperactivity disorder and dyssomnia. J Atten Disord 10(2):217–227

Musser ED, Backs R, Schmitt CF, Ablow JC et al (2011) Emotion regulation via the autonomic nervous system in children with attention-deficit/hyperactivity disorder (ADHD). J Abnorm Child Psychol 39(6):841–852

Nicolaides NC, Charmandari E, Chrousos GP, Kino T (2014) Circadian endocrine rhythms: the hypothalamic–pituitary–adrenal axis and its actions. Ann N Y Acad Sci 1318:71–80

Niederhofer H (2012) Treating ADHD with agomelatine. J Atten Disord 16(4):346–348

Niedermeyer E, Naidu SB (1997) Attention-deficit hyperactivity disorder (ADHD) and frontal-motor cortex disconnection. Clin Electroencephal 28:130–136

Noggle C, Dean R, Horton A (2012) The encyclopedia of neuropsychological disorders. Springer, New York

Ottoni GL, Antoniolli E, Lara DR (2012) Circadian preference is associated with emotional and affective temperaments. Chronobiol Int 29:786–793

Owens JA (2009) A clinical overview of sleep and attention-deficit/hyperactivity disorder in children and adolescents. J Can Acad Child Adolesc Psychiatry 18 (2):92–102

Peppers KH, Eisbach S, Atkins S et al (2016) An intervention to promote sleep and reduce ADHD symptoms. J Pediatr Health Care 30:e43–e48

Phillips AJK, Vidafar P, Burns AC et al (2019) High sensitivity and interindividual variability in the response of the human circadian system to evening light. Proc Natl Acad Sci U S A 116(24):12019–12024

Quach J, Hiscock H, Wake M (2012) Sleep problems and mental health in primary school new entrants: cross-sectional community-based study. J Paediatr Child Health 48:1076–1081

Raman S, Coogan AN (2019) Closing the loop between circadian rhythms, sleep, and attention deficit hyperactivity disorder. In: Dringenberg HC (ed) Handbook of behavioral neuroscience, vol 30. Elsevier, pp 707–716

Randazzo WT, Dockray S, Susman EJ (2008) The stress response in adolescents with inattentive type ADHD symptoms. Child Psychiatry Hum Dev 39:27–38

Roenneberg T, Allebrandt KV, Merrow M, Vetter C (2012) Social jetlag and obesity. Curr Biol 22 (10):939–943

Roenneberg T, Wirz-Justice A, Merrow M (2003) Life between clocks: daily temporal patterns of human chronotypes. J Biol Rhythms 18(1):80–90

Ruben MD, Hogenesch JB, Smith DF (2019) Sleep and circadian medicine—time of day in the neurologic clinic. Neurol Clin 37(3):615–629

Rubia K (2018) Cognitive neuroscience of attention deficit hyperactivity disorder (ADHD) and its clinical translation. Front Hum Neurosci 12:100

Russell VA (2007) Neurobiology of animal models of attention-deficit hyperactivity disorder. J Neurosci Methods 161:185–198

Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD (2006) An open trial of light therapy in adult attention-deficit/hyperactivity disorder. J Clin Psychiatry 67:1527–1535

Rybak YE, McNeely HE, Mackenzie BE, Jain UR, Levitan RD (2007) Seasonality and circadian preference in adult attention-deficit/hyperactivity disorder: clinical and neuropsychological correlates. Compr Psychiatry 48:562–571

Salardini E, Zeinoddini A, Kohi A, Mohammadi MR, Mohammadinejad P, Khiabany M, Shahriari M, Akhondzadeh S (2016) Agomelatine as a treatment for attention-deficit/hyperactivity disorder in children and adolescents: a double-blind, randomized clinical trial. J Child Adolesc Psychopharmacol 26(6):513–519

Sangal RB, Owens J, Allen AJ, Sutton V, Schuh K, Kelsey D (2006) Effects of atomoxetine and methylphenidate on sleep in children with ADHD. Sleep 29 (12):1573–1585

Sciberras E, Mulraney M, Mensah F, Oberklaid F, Efron D, Hiscock H (2019) Sustained impact of a sleep intervention and moderators of treatment outcome for children with ADHD: a randomised controlled trial. Psychol Med 18:1–10

Sivertsen B, Harvey AG, Pallesen S, Hysing M (2015) Mental health problems in adolescents with delayed sleep phase: results from a large population-based study in Norway. J Sleep Res 24(1):11–18

Smith CS, Reilly C, Midkiff K (1989) Evaluation of three circadian rhythm questionnaires with suggestion for an improved measure of morningness. J Appl Psychol 75:728–738

Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkof GA (2001) Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol 16(2):86–92

Snitselaar MA, Smits MG, van der Heijden KB et al (2013) Influence of methylphenidate on circadian rhythmicity and sleep in adult attention-deficit/hyperactivity disorder. Sleep Biol Rhythms 11:282–285

Soehner A, Bertocci MA, Levenson JC et al (2019) Longitudinal associations between sleep patterns and psychiatric symptom severity in high-risk and community comparison youth. J Am Acad Child Adolesc Psychiatry 58–6:608–617

Still G (1902) The Goulstonian lectures on some abnormal psychical conditions in children, Lecture 1. Lancet 1:1008–1012

Sung V, Hiscock H, Sciberras E, Efron D (2008) Sleep problems in children with attention-deficit/hyperactivity disorder: prevalence and the effect on the child and family. Arch Pediatr Adolesc Med 162:336–342

Szeinberg A, Borodkin K, Dagan Y (2006) Melatonin treatment in adolescents with delayed sleep phase syndrome. Clin Pediatr (Phila) 45(9):809–818

Tirosh A, Sadeh R, Munvez P et al (1993) Effects of methylphenidate on sleep in children with attention-deficient hyperactivity disorder An activity monitor study. Am J Dis Child 147:1313–1315

Tjon Pian Gi CV, Broeren JP, Starreveld JS, Versteegh FG (2003) Melatonin for treatment of sleeping disorders in children with attention deficit/hyperactivity disorder: a preliminary open label study. Eur J Pediatr 162 (7–8):554–555

Toplak ME, Jain U, Tannock R (2005) Executive and motivational processes in adolescents with attention deficit-hyperactivity disorder (ADHD). Behav Brain Funct 1(1):8

Tso W, Chan M, Ho FK et al (2019) Early sleep deprivation and attention-deficit/hyperactivity disorder. Pediatr Res 85(4):449–455

Turner-Cobb JM (2005) Psychological and stress hormone correlates in early life: a key to HPA-axis dysregulation and normalisation. Stress 8:47–57

Van der Heijden KB, Smits MG, van Someren EJ, Gunning WB (2005) Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. Chronobiol Int. 22 (3):559–570

Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB (2007) Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry 46(2):233–241

Van Geijlswijk IM, Korzilius HP, Smits MG (2010) The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep 33(12):1605–1614

Van Veen MM, Kooij JJ, Boonstra AM, Gordijn MC, Van Someren EJ (2010) Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry 67 (11):1091–1096

Van West D, Claes S, Deboutte D (2009) Differences in hypothalamic–pituitary–adrenal axis functioning among children with ADHD predominantly inattentive and combined types. Eur Child Adolesc Psychiatry 18:543–553

Viggiano D, Ruocco LA, Sadile AG (2003) Dopamine phenotype and behaviour in animal models: in relation to attention deficit hyperactivity disorder. Neurosci Biobehav Rev 27:623–637

Virkkunen M (1985) Urinary free cortisol secretion in habitually violent offenders. Acta Psychiatr Scand 72:40–44

Voinescu BI, Szentagotai A, David D (2012) Sleep disturbance, circadian preference and symptoms of adult attention deficit hyperactivity disorder (ADHD). J Neural Transm (Vienna) 119(10):1195–1204

Watanabe Y, Fujita M, Ito Y, Okada T, Kusuoka H, Nishimura T (1997) Brain dopamine transporter in spontaneously hypertensive rats. J Nucl Med 38:470–474

Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD (2006) Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. J Am Acad Child Adolesc Psychiatry 45(5):512–519

Xu X, Breen G, Chen CK, Huang YS, Wu YY, Asherson P (2010) Association study between a polymorphism at the 3′-untranslated region of CLOCK gene and attention deficit hyperactivity disorder. Behav Brain Funct 6:48

Yoon SYR, Jain U, Shapiro C (2012) Sleep in attention-deficit/hyperactivity disorder in children and adults: past, present, and future. Sleep Med Rev 16:371–388