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The Circadian System and Sleep in Individuals with ADHD
Cirkadiánní systém a spánek u jedinců s ADHD

Bachelor's Thesis

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Poděkování

Rád bych poděkoval Mgr. Kateřině Skálové, své školitelce, za cenné rady, podporu a přátelský přístup, kterých se mi v průběhu psaní práce dostalo a jichž si nesmírně vážím. Dále také děkuji doc. RNDr. Zdeňce Bendové, Ph.D. za veškeré postřehy k práci i za vstřícnost během studia. Velké poděkování za jazykové korektury patří mému kamarádovi a rodilému Britovi Danielu Jeevesovi, MA. Rovněž si cením pomoci Sabiny Klykorkové s reprodukcí grafu týkajícího se regulace spánku a bdění, který tak mohl být v práci použit v původní podobě. Dále bych chtěl poděkovat své rodině za všechnu podporu během svých studií.

Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 10. 08. 2021

Martin Nejedlý

Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is associated with sleep disorders and abnormalities of the circadian system. In recent studies, ADHD has been linked to late chronotype and delayed sleep phase disorder, clock gene polymorphisms, geographic variation in solar irradiation, longer sleep latency, and impaired sleep quality. However, research findings in children with ADHD often differ from those in adult patients. A new diagnostic category, ADHD-SOM, has been proposed to describe individuals whose symptoms are partially caused by chronic sleep issues. However, most of the evidence is correlational. The thesis summarizes research on sleep and circadian correlates of ADHD and some of the potential mechanisms explaining these associations. Chronotherapy and sleep interventions are promising methods of adjunctive ADHD treatment.

Keywords: Circadian system, ADHD, Sleep, Chronotype, Chronotherapy

Abstrakt

Porucha pozornosti s hyperaktivitou (ADHD) je spojována s poruchami spánku a abnormalitami cirkadiánního systému. Studie z posledních let poukazují na souvislosti s pozdním chronotypem a syndromem opožděné spánkové fáze, polymorfismy hodinových genů, geografickou variabilitou v intenzitě slunečního záření, delší spánkovou latencí a narušenou kvalitou spánku. Výzkumy prováděné s dětskými a dospělými pacienty se však mnohdy neshodují ve svých závěrech. Přestože byla navržena nová diagnostická kategorie ADHD-SOM označující jedince, u kterých je část symptomů způsobena chronickými spánkovými potížemi, většina důkazů je korelační povahy. Práce shrnuje výzkumná zjištění týkající se cirkadiánních a spánkových korelátů ADHD a některé potenciální mechanismy, kterými by tyto koreláty mohly být s poruchou spojeny. Chronoterapie a spánkové intervence představují slibné metody v podpůrné léčbě ADHD.

Klíčová slova: Cirkadiánní systém, ADHD, Spánek, Chronotyp, Chronoterapie

Acronyms and Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-SOM	ADHD-somnus clinical presentation
ARAS	ascending reticular activating system
AVP	arginine vasopressin
BLT	bright light therapy
BMAL1/*Bmal1*/BMAL1	brain and muscle ARNT-like 1 human gene / rodent gene / protein
cAMP	cyclic adenosine monophosphate
CAP	cyclic alternating pattern
CAR	cortisol awakening response
CCG	clock-controlled gene
Chrono	ChIP-derived repressor of network oscillator rodent gene
*CK1/Ck1/*CK1 ε/δ	Casein kinase 1 human gene / rodent gene / protein ε/δ
*CLOCK/Clock/*CLOCK	circadian locomotor output cycles caput human gene / rodent gene / protein
CPT	continuous performance test
CREB	cAMP-response element binding protein
*CRY/Cry/*CRY 1/2	cryptochrome human gene / rodent gene / protein 1/2
DLMO	dim light melatonin onset
DMH	dorsomedial hypothalamic nucleus
dmSCN	dorsomedial suprachiasmatic nucleus
DRD/*Drd/*DRD 4	dopamine receptor D4 human gene / rodent gene / protein
DRD4 7R/DRD4 7R	*DRD4/*DRD4 7-repeat polymorphism
DSM-IV/DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 4th/5th revision
DSPD	delayed sleep phase disorder
E-box	enhancer box
EEG	electroencephalography
FBXL3	F-box/leucine-rich repeat protein 3 human gene
GABA	γ-Amino-Butyric-Acid
GHT	geniculohypothalamic tract
GWAS	genome-wide association studies
HPA (axis)	hypothalamic-pituitary-adrenal (axis)
IGL	intergeniculate leaflet
ipRGCs	intrinsically photosensitive retinal ganglion cells
LC	locus coeruleus
MCTQ	Munich ChronoType Questionnaire
MEQ	Morningness-Eveningness Questionnaire
MSF_{SC}	midpoint of sleep on free days corrected for sleep debt
MT_1	melatonin receptor type 1A
MT_2	melatonin receptor type 1B
N1-3	non-REM sleep stage 1-3
NPY	neuropeptide-Y
Nr1d1	nuclear receptor subfamily 1 group D member 1
Nr1d2	nuclear receptor subfamily 1 group D member 2
NT	neurotransmitter
ODD	Oppositional Defiant Disorder
PACAP	pituitary adenylate cyclase-activating polypeptide
PDE4D	phosphodiesterase 4D
PER/Per/PER 1/2/3	period human gene / rodent gene / protein 1/2/3
PET	positron emission tomography
PFC	prefrontal cortex
PGN	pregeniculate nucleus
PI3Kγ/PI3Kγ	phosphoinositide 3-kinase gamma gene / protein
PPT-LDT	pedunculopontine and laterodorsal tegmental nuclei

PSG	polysomnography
PVN	paraventricular nucleus
REM	rapid eye movement
RHT	retinohypothalamic tract
ROR	retinoic acid receptor-related orphan receptor
RORE	ROR/REV-ERB binding element
SCN	suprachiasmatic nucleus
SD	standard deviation of the mean
SI	solar irradiance
SNP	single-nucleotide polymorphism
SPZ	subparaventricular zone
SWA	slow-wave activity
SWS	slow-wave sleep
UTR	untranslated region
VIP	vasoactive intestinal peptide
VLPO	ventrolateral preoptic area
vlSCN	ventrolateral suprachiasmatic nucleus

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1 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder affecting 5 % of children and 2.5 % of adults. It is defined by symptoms of hyperactivity/impulsivity and/or inattention. Individuals with ADHD also show deficits in executive functions. By definition, the symptoms impair everyday functioning in multiple areas.

Extreme chronotype is a commonly reported trait in adult patients with ADHD. Approximately 33 % of adults with ADHD suffer from the delayed sleep phase disorder (DSPD). Rare variants of clock genes that are strongly associated with both DSPD and ADHD have recently been discovered.

Individuals with ADHD often experience sleep issues. Sleep disturbances have been reported by approximately 73 % of child patient caregivers. Common complaints include insomnia, lower sleep quality, and greater daytime sleepiness. Sleep disturbances are also known to impair attention in the general population and worsen ADHD symptoms.

In the past two decades, circadian abnormalities and sleep issues in patients with ADHD have received a considerable amount of interest. ADHD-SOM is a newly proposed diagnostic category where a portion of ADHD symptoms is mediated by the impairment of sleep. However, most of the cited research is correlational and different outcomes have been reported in children and in adults.

The aim of this thesis is to summarise the research on circadian abnormalities and sleep issues that have been most studied in patients with ADHD. Special emphasis will be placed on distinguishing the available evidence in children and in adults. Where relevant, some of the hypothesized pathophysiological pathways will be briefly mentioned.

The first two chapters are introductory and attempt to provide the necessary theoretical context. The main principles of the circadian system are presented first. Next, the second chapter deals with sleep and wakefulness, particularly with sleep physiology, its regulation, and also some of its relevant circadian aspects such as melatonin and chronotype. Although research on the general principles of circadian and sleep physiology has been primarily conducted in animal models, studies examining the generalisability of the mechanisms to human subjects will be shortly presented as well. The third chapter then sets these general principles into the context of ADHD and reviews the associated abnormalities. Additionally, a section on chronotherapy and sleep-focused interventions follows and asks if they improve ADHD symptoms.

2 The Circadian System

2.1 Circadian Rhythms

Organisms possess the ability to adapt to changes in their external environment. As some of these changes tend to be periodic, adjusting physiological processes in a corresponding manner provides an evolutionary advantage. These adaptative periodic phenomena are called biological rhythms (Reinberg & Ashkenazi, 2003*).

A diurnal rhythm presents an encompassing term for all biological rhythms with a period of approximately 24 hours, which is directly related to the light-dark cycle on Earth determined by the Earth's rotation around its axis[1]. Some of these rhythms are endogenous in nature, that is, they are not a mere response to environmental stimuli and are maintained even under constant external conditions. Such diurnal rhythms are called circadian rhythms. The word "circadian" originates from the Latin *circa diem*, meaning "approximately a day" (Vitaterna et al., 2001*).

Despite the fact that circadian rhythms are driven by endogenous mechanisms, they require exogenous signals (*zeitgebers*) to be synchronised with the Earth's rotation cycle. In an environment absent of zeitgebers, adults have, on average, a free-running period of 24 hours and 11 minutes (SD = 8 minutes) and therefore the internal clock phase tends to become delayed with respect to the solar day (Czeisler et al., 1999). The internal clock can be entrained by both photic (light exposure and its variations) and non-photic stimuli, with the latter including food consumption, motor activity, social cues, and others (Reinberg & Ashkenazi, 2003*).

2.2 Organisation of the Circadian System

The mammalian circadian system shows a functional hierarchy with a central oscillator synchronising peripheral clocks. An extensive series of experiments have demonstrated that the circadian pacemaker (also called the *master synchroniser*) is the suprachiasmatic nucleus (SCN), a bilaterally paired structure located in the anterior hypothalamus above the optic chiasm. For instance, lesions in this area have been shown to result in the loss of rhythmicity in various types of processes in rodents, such as hormonal secretion, motor activity and body temperature (Moore & Eichler, 1972; Refinetti et al., 1994). In addition, SCN transplantations are not only able to restore circadian rhythmicity, but also establish a donor's circadian period in the recipient's rhythms (Ralph et al., 1990). Indirect evidence supporting the central role of the SCN in human circadian rhythmicity comes from case studies of anterior hypothalamic lesions (Cohen & Albers, 1991; Schwartz et al., 1986) and studies showing associations between SCN degeneration and the disruption of circadian rhythms (Hofman & Swaab, 1994; Stopa et al., 1999).

The rodent SCN can be divided into two anatomically as well as functionally distinct regions – a ventrolateral part (vlSCN, "core") with a predominance of the neurotransmitter (NT) vasoactive intestinal peptide (VIP) and a dorsomedial part (dmSCN, "shell") with neurons containing arginine vasopressin (AVP). The core also includes gastrin releasing peptide cells, and another NT, γ-Amino-Butyric-Acid (GABA), is

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[1] More precisely, the Earth's rotation period is 23 hours 56 minutes and 4 seconds.

expressed by most neurons in both areas (Moore et al., 2002*). Mai et al. (1991) have reported similar organisation of the human SCN with central and dorsal subdivisions showing comparable neurochemical features to those of vlSCN and dmSCN, respectively.

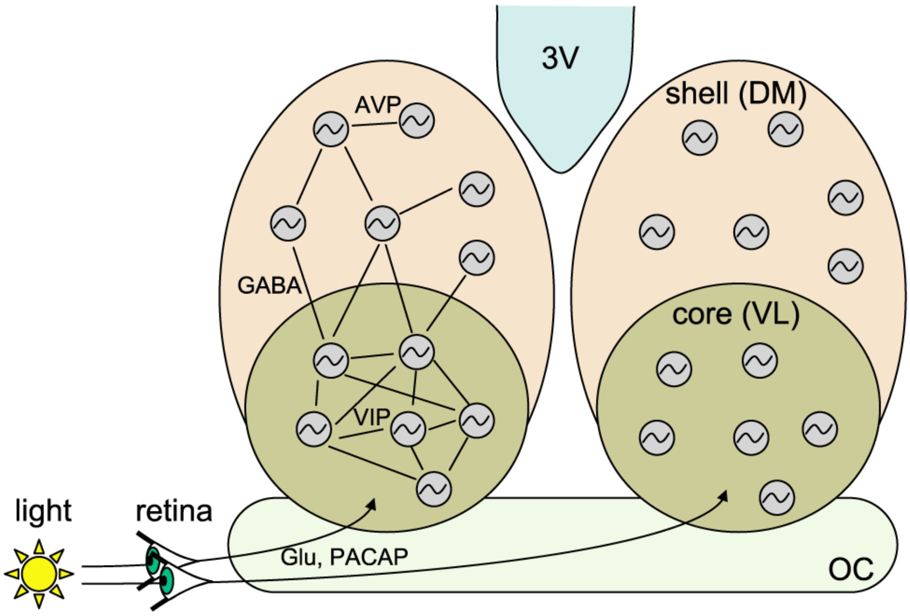

Figure 1: Scheme of the SCN. *Note:* The SCN lies above the OC and has two distinct parts – core and shell. The core receives photic inputs from the retina via a glutamatergic pathway (RHT) and its neurons express VIP, which also relays information to the shell. The shell expresses mainly AVP. AVP = arginine vasopressin; DM = dorsomedial part; GABA = γ-Amino-Butyric-Acid; Glu = glutamate; PACAP = pituitary adenylate cyclase-activating polypeptide; VIP = vasoactive intestinal peptide; VL = ventrolateral part; OC = optic chiasm; 3V = third ventricle, Reprinted from Hafner et al. (2012, p. 2). Licensed under CC BY 4.0.

Welsh et al. (1995) demonstrated that neurons of the rodent SCN are capable of autonomous oscillations in their firing rates. Neuronal connections are required for the production of a coherent output in electrical activity (Honma et al., 2000). Both parts of the SCN receive direct photic inputs from the retina via the retinohypothalamic tract (RHT). Nevertheless, the RHT fibers are denser in the vlSCN. As shown in Figure 1, the signals are being relayed from its VIP neurons to the AVP neurons of the dmSCN (Lokshin et al., 2015; Varadarajan et al., 2018).

Three main pathways bring input to the SCN (Figure 2). As has already been mentioned, the RHT originates from the retina, more specifically from a subgroup of its ganglion cells called intrinsically photosensitive retinal ganglion cells (ipRGCs) which contain the photopigment melanopsin that is most sensitive to blue light (λ_{max} = 480 nm) wavelengths (Berson et al., 2002; Hannibal et al., 2004). It travels as part of the optic nerve and continues through the optic chiasm into the SCN in a monosynaptic manner, mainly into its anteroventral part in humans (Dai et al., 1998b). In mice, it has been demonstrated that the RHT is essential for the entrainment of the circadian clock with the light-dark cycle (Wee et al., 2002). Its main NT is glutamate. The pituitary adenylate cyclase-activating polypeptide (PACAP) co-occurs in some of the glutamatergic synapses and enhances its effects (Hannibal et al., 2000).

The retinal axons also project to the lateral geniculate nucleus where they synapse on the intergeniculate leaflet (IGL) neurons. The rodent IGL is the origin of the second pathway called the geniculohypothalamic tract (GHT), which carries inputs to the SCN via neuropeptide-Y (NPY) neurons (Moore & Card, 1994) and GABA (Hanna et al., 2017). This pathway integrates the photic and non-photic stimuli, such as physical activity, and contributes to the SCN entrainment (Biello et al., 1994; Hanna et al., 2017). In primates, IGL has its homologue in the subset of the pregeniculate nucleus (PGN). However, the existence of GHT in higher primates, including humans, has been questioned (Chevassus-au-Louis & Cooper, 1998).

A third SCN afferent pathway studied on animal models stems from the median raphe nucleus and its serotonergic portion is involved in non-photic phase shifting (Yamakawa & Antle, 2010).

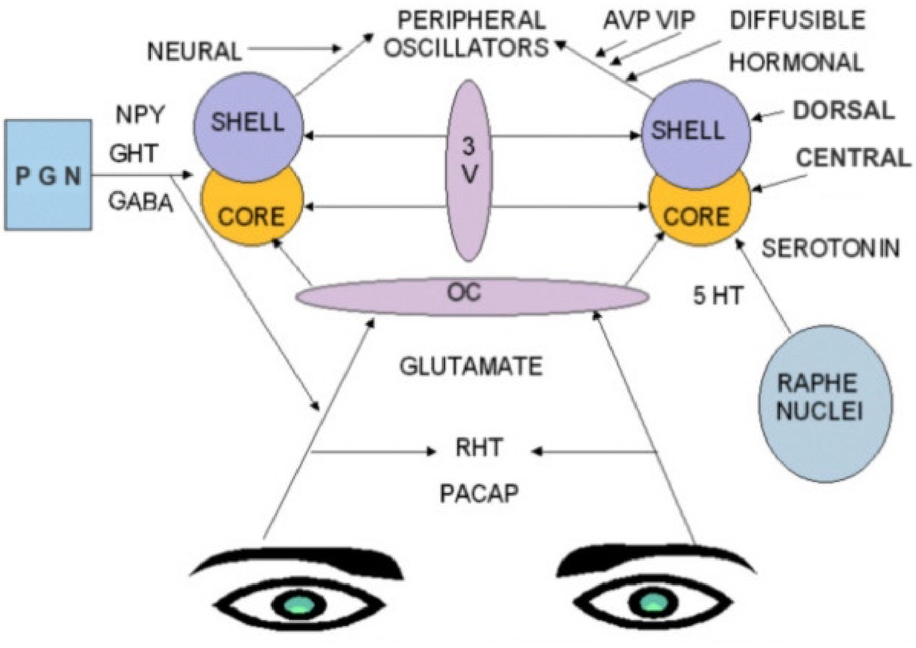

Figure 2: Afferent inputs of the SCN. *Note:* Three pathways bring input to the SCN. The glutamatergic RHT monosynaptically carries signals from the ipRGCs sensitive to blue light wavelength. The GHT uses NPY as well as GABA and stems from the IGL/PGL. The third pathway is serotonergic and stems from the raphe nuclei. AVP = arginine vasopressin; GABA = γ-Amino-Butyric-Acid; GHT = geniculohypothalamic tract; NPY = neuropeptide-Y; OC = optic chiasm; PGN = pregeniculate nucleus; RHT = retinohypothalamic tract; VIP = vasoactive intestinal peptide; 3V = third ventricle; 5 HT = 5-hydroxytryptamine (serotonin), Adapted from Reghunandanan and Reghunandanan (2006*, p. 3). Licensed under CC BY 2.0.

The SCN itself is connected to a variety of neural structures, including the hypothalamus, thalamus, and possibly others. These connections allow for the timekeeping signal transduction to the whole body (Dibner et al., 2010*). Rodent studies have shown that SCN projections to the paraventricular nucleus (PVN) of the hypothalamus are involved in the circadian regulation of hormonal secretion (Buijs et al., 1993; Ono et al., 2020). A multisynaptic pathway starting with a GABAergic SCN-PVN connection terminates on the pineal gland and is responsible for the rhythmic production of melatonin (Kalsbeek et al., 2000). Apart from the hormonal pathways, the PVN also mediates the circadian signal transmission to the peripheral organs through autonomic nervous connections (Buijs et al., 1999; Kalsbeek, 2004). SCN also projects onto the subparaventricular zone (SPZ) of the hypothalamus (Abrahamson & Moore, 2001). Whilst the dorsal SPZ has been implied in the circadian rhythm in body temperature, the ventral SPZ is related to the sleep-wakefulness cycle and the rhythm in motor activity (Lu et al., 2001). Dai et al. (1998a) have confirmed the existence of both the SCN-PVN and the SCN-SPZ connections in the human brain.

Peripheral oscillators are present in most tissues (for an overview, see Zhang et al., 2020*). The synchronisation between the peripheral tissues requires inputs from the central clock. It was originally thought that the absence of the SCN would not only lead to phase desynchronisation between peripheral organs, but also result in the loss of rhythmicity at a single organ level due to the lack of intercellular connections capable of coupling the rhythms of individual cells. The latter assumption has recently been challenged as studies in mice have demonstrated the capacity of the liver and possibly other organs to produce and sustain autonomous rhythms in the absence of the SCN and zeitgebers (Sinturel et al., 2021).

Unlike in the central clock with light being the main zeitgeber, the feeding schedule can serve as the main mechanism of entrainment for the peripheral clock. Feeding signals may cause their uncoupling from the circadian phase of the SCN (Damiola, 2000). A recent laboratory trial supports the role of food as zeitgeber for peripheral oscillators as well as the possibility of uncoupling in humans (Wehrens et al., 2017).

2.3 The Molecular Mechanism of the Circadian System

An underlying molecular mechanism that determines the endogenous nature of circadian rhythms is the expression of clock genes and their interactions through feedback loops within individual cells (Figure 3). In mammals, the main transcription-translation negative feedback loop consists of "core" clock genes that involve negative elements *Period* (*Per1, Per2, Per3*), *Cryptochrome* (*Cry1, Cry2*) and positive elements *Clock* and *Bmal1* (Takahashi, 2017*). Goriki et al. (2014) have also described an additional negative element *Chrono*.

At the start of the subjective day[2], the CLOCK:BMAL1 heterodimer protein binds to a DNA responsive element E-box which activates the transcription of *Per* and *Cry* (Jin et al., 1999; Kume et al., 1999; Lee et al., 2001). PER and CRY accumulate in the cytoplasm at around the beginning of the subjective night and are translocated into the nucleus where they repress *Clock* and *Bmal1* transcription. As fewer CLOCK:BMAL1 heterodimers are produced, *Per* and *Cry* transcription is inhibited as well. PER and CRY are also actively degraded by the proteasome and eventually the loop returns to its original state with the initial *Clock* and *Bmal1* expression (Busino et al., 2007; Eide et al., 2005; Lee et al., 2001; Sato et al., 2006).

The main feedback loop timing is also dependent on posttranslational modifications. Casein kinases 1ε/1δ (CK1ε/δ) phosphorylate PER1/2 (Lee et al., 2001). The site of the phosphorylation determines the overall effect, which can either target the protein for proteasome degradation, or for the translocation into the nucleus (Vanselow et al., 2006). The CK1-mediated PER1/2 degradation is responsible for the delay between the mRNA and the protein peak accumulation (Lee et al., 2001). The homozygous $Ck1\varepsilon^{Tau}$ mutation in hamsters results in the shortening of the free-running period from approximately 24 hours to 20 hours (Lowrey et al., 2000). *CK1δ* and *PER2* phosphorylation site mutations have been found in human families with familial advanced sleep phase syndrome characterised with an early evening sleep onset and the shortening of the circadian period (Toh, 2001; Vanselow et al., 2006; Xu et al., 2005).

An additional stabilising feedback loop involves clock genes coding for nuclear receptors REV-ERBα (*Nr1d1)*, REV-ERBβ *(Nr1d2)* and RORα/β/γ (Takahashi, 2017*). They all competitively bind to the promoter of *Bmal1,* specifically to the REV-ERB/ROR binding elements (ROREs). Whilst the REV-ERBs act as repressors of *Bmal1*, RORs function as its activators (Guillaumond et al., 2005). As genes for REV-ERBα/β contain E-box, CLOCK:BMAL1 activates their expression, which in turn results in *Bmal1* repression (Triqueneaux et al., 2004; Yang et al., 2013).

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[2] Subjective day and subjective night are terms used to describe a specific part of the circadian cycle of an organism irrespective of the objective time of the day, as they might not always be synchronised. For more details on the timing of the described events, see Lee et al. (2001).

The circadian molecular machinery directly influences other cellular processes. Clock-controlled genes (CCGs) are not necessary for the circadian mechanism but are activated or repressed by the clock gene products. CCGs regulate a plethora of physiological functions and may be tissue specific (Bozek et al., 2009). Their circadian regulation may occur via the inclusion of E-box or RORE in their promoters (Ueda et al., 2005).

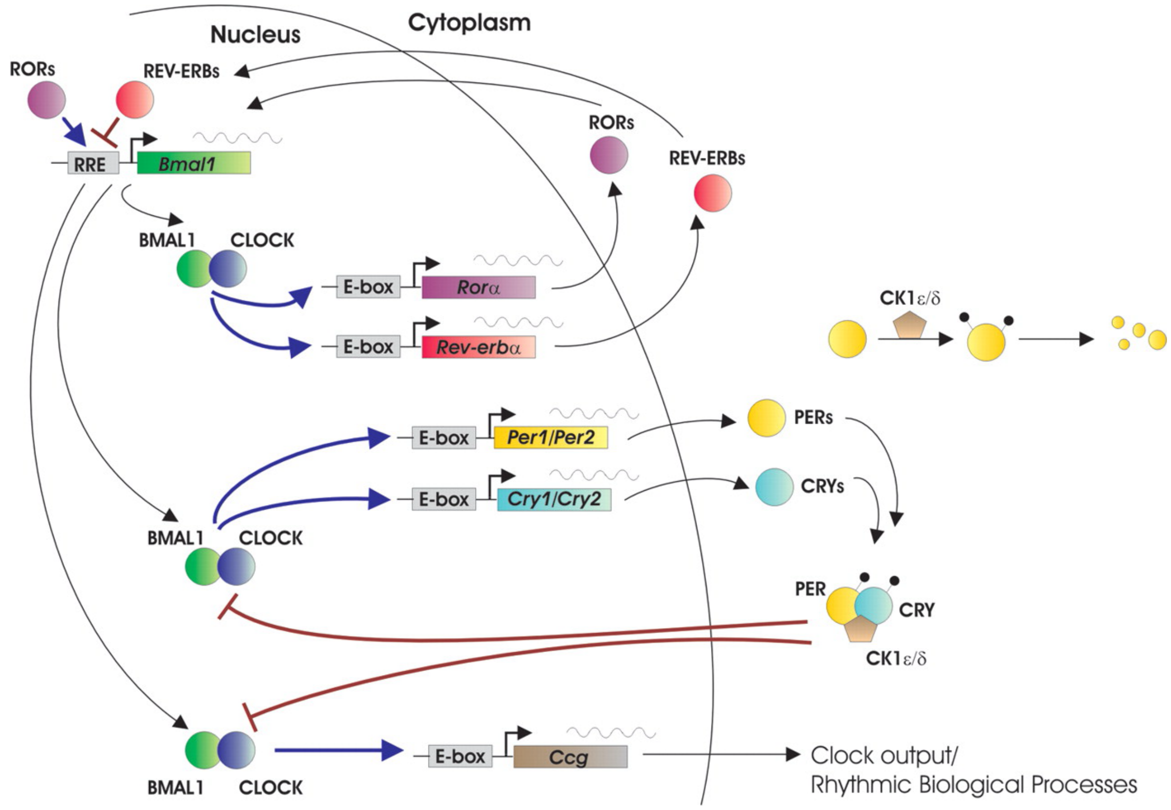

Figure 3: Fundamental molecular mechanisms of the mammalian circadian clock. *Note:* Clock genes and their interactions through transcription-translation feedback loops are the molecular basis of the circadian rhythmicity (for explanation, see the main text). *Bmal1*/BMAL1 = *brain and muscle ARNT-like 1* gene / protein; Ccg = clock-controlled genes; CK1ε/δ = Casein kinases 1ε/1δ; CLOCK = circadian locomotor output cycles caput protein; *Cry*/CRY *1/2* = *Cryptochrome 1/2* genes / proteins; E-box = enhancer box; *Per*/PER 1/2 = *Period 1/2* gene / protein; ROR = retinoic acid receptor-related orphan receptor; RRE = REV-ERB/ROR binding element (RORE in the main text). Reprinted from Ko and Takahashi (2006*, p. R272). Copyright 2006 by Oxford University Press. Reprinted with permission.

The molecular mechanism of the circadian clock is highly conserved in mammals (Isojima et al., 2003*). Apart from the aforementioned effects of the *CK1δ* and *PER2* mutations on the human circadian period length (Toh, 2001; Xu et al., 2005), an additional study has also found a *CRY1* mutation in families with the delayed sleep phase disorder (DSPD; Patke et al., 2017). Genome-wide association studies (GWAS) have demonstrated associations of a self-reported chronotype[3] with various clock gene polymorphisms and genetic loci known to be involved in circadian rhythmicity in mammals, such as *PER2* and *FBXL3* (Jones et al., 2016; Lane et al., 2016). Another recent GWAS has confirmed these findings on a larger sample and extended them with additional gene associations, including *CRY1* and *PER1*. An additional analysis from the same study also showed that lead chronotype-related gene variants were associated with sleep timing measured by actigraphy (Jones et al., 2019).

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[3] For more details on chronotype, see the next chapter.

3 Sleep and Wakefulness

The sleep-wake cycle is a biological rhythm with a circadian regulation. On a behavioural level, sleep is a reversible state that can be defined using descriptors such as perceptual alterations (disengagement) and a lack of responsiveness to environmental stimuli. In laboratories, human sleep is usually measured using polysomnography, a method combining electroencephalography (a method using electrodes on the scalp measuring neural oscillations; EEG), electrooculography (measuring eye movements) and electromyography (measuring electrical activity in skeletal muscles; Carskadon & Dement, 2017*).

3.1 Sleep Architecture

Sleep can be further decomposed into individual units, sleep cycles. During an uninterrupted 8hour sleep of healthy adults, three to five sleep cycles take place. A full sleep cycle lasts approximately 90-120 minutes and consists of two broad stages: rapid eye movement (REM) sleep and non-rapid eye movement (non-REM) sleep (Figure 4; Carskadon & Dement, 2017*).

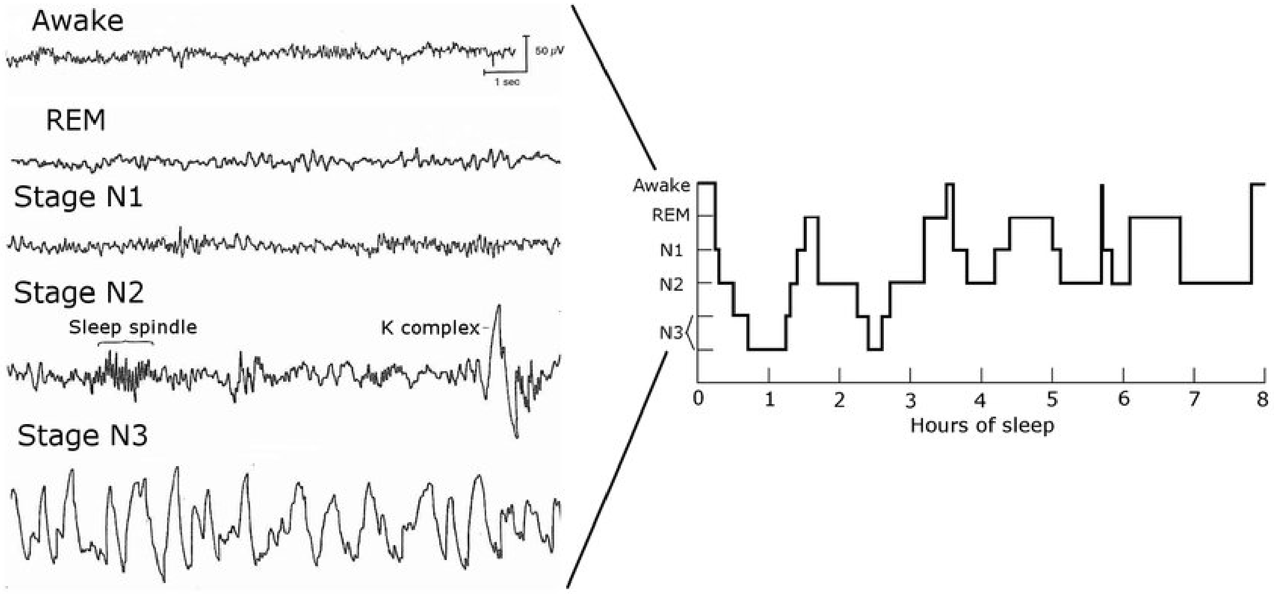

Figure 4: Sleep Architecture and EEG Patterns of Sleep Stages in Healthy Adults. *Note:* Three to five sleep cycles repeat during the night. A typical sleep cycle progresses in the following way: N1 -> N2 -> N3 -> N2 -> REM. In the second half of the night, REM sleep lasts longer and N3 sleep is reduced. N1-3 = non-REM stage 1-3; REM = rapid eye movement. Reprinted from Fink (2012*, p. 36).

Non-REM sleep consists of three stages (N1-3, previously also N4). N1 (light sleep) is the transitional state between wakefulness and sleep. In N2, sleep becomes deeper and eye movements diminish, although subjects can still be easily awakened. K-complexes (sharp slow waves) appear, often followed by sleep spindles (short neural activity of 11 – 16 Hz). In N3, delta waves (0.5 – 2 Hz in terms of sleep standards) become frequent (> 20 %) and correspond to slow-wave sleep (SWS). Individuals cease to respond to common environmental stimuli. Non-REM sleep typically starts with N1 followed by N2, which then progresses to N3. After that, it reverts to N2 and REM sleep follows next. This sequence of events comprises a full sleep cycle. Most of the N3 stages occur during the first half of the night. In the second half, REM sleep is longer and may follow N2 directly. REM sleep is more energetically demanding. Apart from the rapid eye movements, its main characteristics are muscle atonia and an EEG profile resembling the state of wakefulness. Dreams that occur at this stage are more vivid (Carskadon & Dement, 2017*; Minkoff, 2016*).

Sleep macrostructure is generally inferred from analysing summaries of 30-second epochs of continuous recordings. However, some patterns, including the sleep spindles and K-complexes, last for short periods of time and require distinct analytic approaches. In total, these phenomena create the sleep microstructure (also called microarchitecture). Of special interest are the cyclic alternating pattern (CAP) cycles. In non-REM, CAP cycles are short events comprised of a distinct activity pattern in phase A followed by an intermittent phase B. For instance, phase A can typically include slower high voltage waves (such as K-complexes) followed by a lower amplitude sleep background activity in phase B. CAP rates in non-REM usually increase when sleep is disturbed and may serve as a marker of sleep instability. Increased CAP rates correlate with sleep quality impairment and subjective reports of sleep issues (Parrino et al., 2012*).

3.2 Neurobiology of Sleep and Wakefulness

Moruzzi and Magoun (1949) were the first to identify the ascending reticular activating system (ARAS) as the key pathway for cortical arousal in cats. Animal studies have described two main branches of ARAS (Figure 5). The first portion originates in the pedunculopontine and laterodorsal tegmental nuclei (PPT-LDT) of the brainstem. It then continues into the thalamus where it cholinergically activates thalamocortical transmission (Hallanger et al., 1987; Saper et al., 2001*). The PPT-LDT are most active in their firing rates during wakefulness and in REM sleep (El Mansari et al., 1989). The second branch of ARAS stems from multiple monoaminergic nuclei in the brainstem and the hypothalamus, including the noradrenergic locus coeruleus, serotonergic dorsal and median raphe nuclei, histaminergic tuberomammillary nuclei of the hypothalamus, and others. This portion projects into the basal forebrain, lateral hypothalamus, and the cerebral cortex. Whilst also being most active during wakefulness, the monoaminergic nuclei firing rates stop during REM sleep (Saper et al., 2001*).

The ventrolateral preoptic area (VLPO) is often described as the sleep-initiating structure as shown in Figure 5. It inhibits ARAS as its sleep-promoting and sleep-active neurons send GABAergic and galaninergic inhibitory connections to the monoaminergic nuclei (Chung et al., 2017; Steininger et al., 2001). The connections are reciprocal, and therefore, VLPO and ARAS inhibit each other's activity and function in a mutually exclusive on/off manner (Chou et al., 2002; Saito et al., 2018).

Orexin-producing neurons found in the lateral hypothalamus support this system and stabilize wakefulness. They project into VLPO (although the VLPO orexin receptors are scarce) and also into both the monoaminergic and cholinergic parts of ARAS (Marcus et al., 2001; Peyron et al., 1998). Orexin-deficient mice and dogs with mutations in orexin receptor 2 gene exhibit signs of narcolepsy (Chemelli et al., 1999; Lin et al., 1999). Orexin signalling in the basal forebrain also seems to be involved in attention shifting as orexin A infusions may enhance cognitive performance in rats (Zajo et al., 2016).

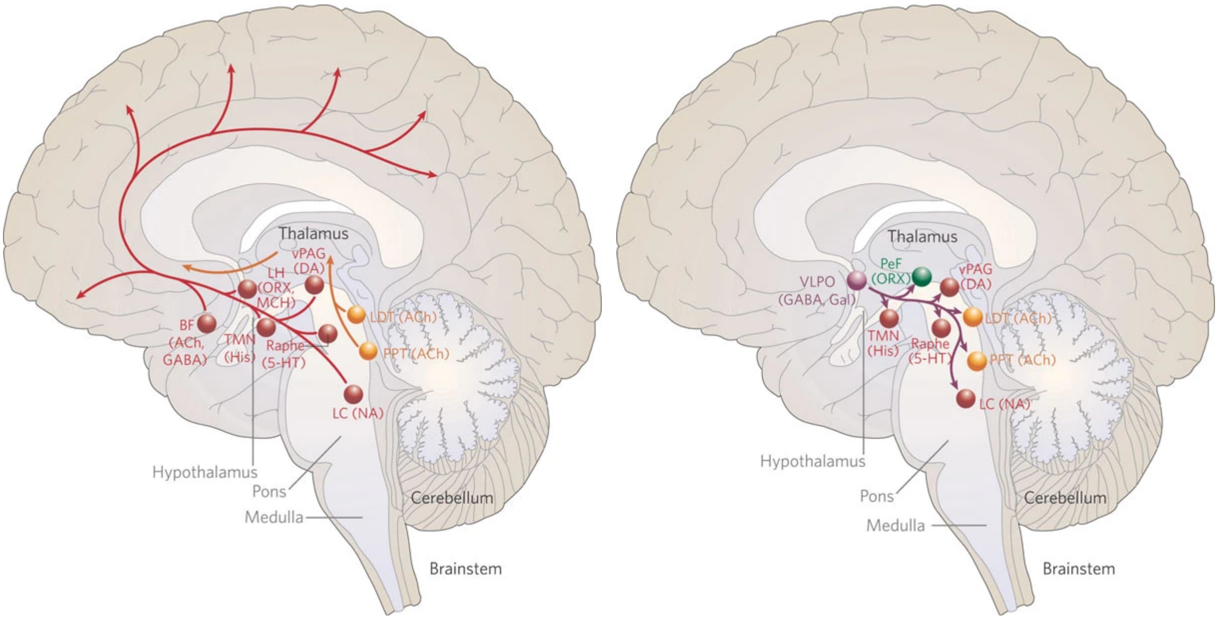

Figure 5: Brain Structures Involved in the Generation of Sleep and Wakefulness. *Note:* The ARAS consists of two branches (left image). The first one stems from PPT/LDT and is cholinergic. It projects into the thalamus where it synapses and continues into the cortex. The second branch includes several monoaminergic nuclei (LC, Raphe, vPAG, TMN), has connections with the basal forebrain and continues diffusely into the cortex. During sleep, VLPO (the intermediate nucleus in humans) inhibits ARAS through its GABAergic and galaninergic projections (right image). Ach = acetylcholine; BF = basal forebrain; DA = dopamine; GABA = γ-Amino-Butyric-Acid; Gal = galanine; His = histamine; LC = locus coeruleus; LDT = laterodorsal tegmental nucleus; LH = lateral hypothalamus; MCH = melanin-concentrating hormone; NA = noradrenaline; ORX = orexins; PeF = perifornical area; PPT = pedinculopontine nucleus; Raphe = median raphe nucleus; TMN = tuberomammillary nucleus; vPAG = ventral periaqueductal gray matter; 5 HT = 5-hydroxytryptamine (serotonin). Reprinted from Saper et al. (2005*, p. 1258). Copyright 2005 by Nature Publishing Group. Reprinted with permission.

Human studies provide partial support for the extrapolation of the outlined neurobiological mechanisms. Human cholinergic neurons of the reticular formation show the greatest density around PPT-LDT (Mesulam et al., 1989). A PET imaging study conducted on healthy volunteers has demonstrated that during the awakening from sleep, cortical activation follows the activation of the brainstem and the thalamus (Balkin, 2002). Using diffusion tensor imaging, various components of the human ARAS have been successfully reconstructed (Jang & Kwon, 2015; Yeo et al., 2013). However, some human-specific connectivity has been reported, namely the ARAS portion stemming from the tegmental area showed additional branching (Edlow et al., 2012). The human brain seems to have a homologue of VLPO which is the intermediate nucleus. The loss of galaninergic neurons in this area has been linked to sleep fragmentation (Lim et al., 2014). There is also some evidence for the wakefulness-stabilising role of the human orexin system. Orexin-related mutations similar to those reported in dogs are rare in humans but narcolepsy has been associated with the degeneration of orexin-producing neurons (Peyron et al., 2000; Thannickal et al., 2000). A small placebo-controlled trial used intranasal orexin-A application in patients with narcolepsy and showed a subsequent reduction in one of the symptoms, wake to REM transitions (Baier et al., 2011). A similar study further corroborated these results and also found that orexin-A application improved performance on a divided attention task that is sensitive to fatigue (Weinhold et al., 2014).

3.3 Sleep and Wakefulness regulation

Borbély (1982*) proposed a famous two-process model of sleep regulation (Figure 6). Process S (homeostatic process) is a sleep debt that increases during the day with the length of wakefulness. It is directly related to sleep intensity rather than to sleep duration and expresses a propensity towards SWS. Process C is a drive for wakefulness that is controlled by the central pacemaker. Under sleep deprivation, Process S continues rising (upper S curve starting at 23:00 in Figure 6). However, even when sleep deprived, fatigue oscillates throughout the day depending on the circadian drive (the Process C curve is an inverse function of these fatigue oscillations, therefore marked as $\bar{C}$ in Figure 6). Process C sets a sleep threshold. For an entrained clock, this threshold rises to its maximum in the afternoon (individuals tend to be the least tired when controlling for Process S) and is at its trough in the second half of the night when body temperature is at its lowest point and REM sleep is the longest. The Process S crosses the threshold set by the Process C upon awakening (around 6 AM in Figure 6).

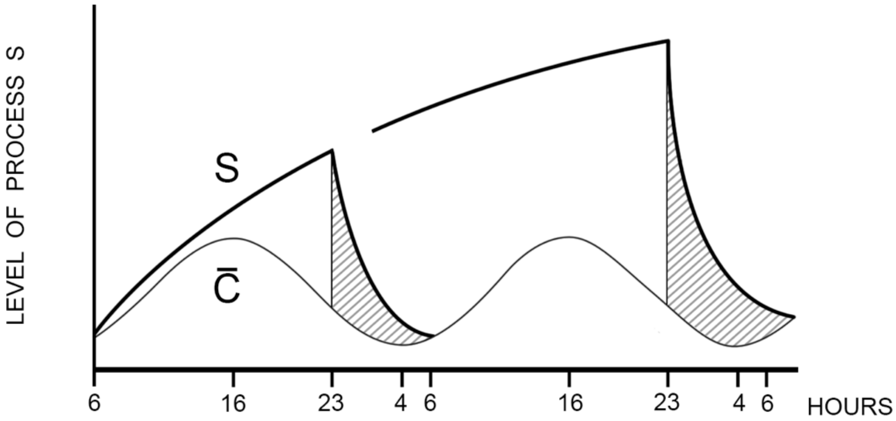

Figure 6: The Two Process Model of Sleep and Wakefulness Regulation. *Note:* The homeostatic sleep drive (Process S) rises during wakefulness and sharply declines following the onset of sleep. The circadian arousal drive (Process C) is regulated by the internal clock and determines the sleep threshold. During the time of awakening, the Process S reaches the lower threshold set by the Process C. The figure also shows an alternative scenario where the Process S keeps increasing in case of sleep deprivation and then drops the next night during sleep. Reproduced from Borbély (1982*, p. 199). Copyright 1982 by Springer. Reproduced with permission.

There are candidates for the neural substrate of the two processes regulating sleep and wakefulness. Adenosine is a NT that signals fatigue. During wakefulness, it accumulates extracellularly in the basal forebrain and also disinhibits VLPO (Chamberlin et al., 2003; Peng et al., 2020). Evidence in humans also connects adenosine to Process S. Polymorphisms in adenosine deaminase (an enzyme degrading adenosine) has been associated with both SWS duration and SWS intensity (Retey et al., 2005). Caffeine is an adenosine-receptor antagonist that delays the onset of sleep and reduces SWS (Landolt, 1995).

The Process C is likely mediated via direct and indirect pathways. The SCN has direct projections to the orexin-producing neurons (Abrahamson et al., 2001). The indirect pathway involves the connections of the SCN with the dorsomedial hypothalamic nucleus (DMH). The DMH then connects to various structures involved in sleep and wakefulness, including VLPO (Chou et al., 2002), the orexinergic neurons (Yoshida et al., 2006), and the noradrenergic locus coeruleus (Aston-Jones et al., 2001).

3.4 Melatonin, Cortisol and the Sleep-Wake Cycle

As has been mentioned, one of the hormonal inputs that provide means of synchronisation between the central and the peripheral clock is the production of melatonin. Melatonin is under the rhythmic regulation of the SCN (the SCN-pineal gland multisynaptic pathway) and is released into the blood (Kalsbeek et al., 2000). In turn, it binds to its receptors that are present within most body tissues, including the SCN (Naji et al., 2004). Two types of melatonin receptors have been identified in humans (MT_1 and MT_2) and they both belong to the G protein-coupled receptor family (Reppert et al., 1994, 1995).

Under dim lighting conditions, melatonin secretion starts approximately two to three hours prior to the person's bedtime (the dim light melatonin onset, DLMO). Melatonin usually peaks in the early morning hours. After that, it gradually declines throughout the rest of the night. Melatonin profiles tend to vary for different individuals. Due to melatonin's short half-life, its blood and saliva concentrations reflect adequately the current state of the central clock. For these reasons, melatonin is commonly used as a biological marker for the circadian phase in human studies (Burgess & Fogg, 2008; Rzepka-Migut & Paprocka, 2020*).

Melatonin induces phase shifts of the circadian clock. In humans, a 0.5 mg quantity shows its peak phase-advancing effects when taken approximately 2 – 4 hours prior to the DLMO and its maximal phase-delaying effects when taken shortly after awakening (Burgess et al., 2010). Due to these actions related to the Process C, melatonin has been indicated for the treatment of DSPD (van Geijlswijk et al., 2010) as well as secondary sleep disorders (Li et al., 2019).

Melatonin is not essential for sleep. Pinealectomy is not associated with disrupted sleep in rats (Fisher & Sugden, 2010). One study of a limited sample size showed that the sleep disruption in patients after pinealectomy was not greater than the sleep disruption in patients that underwent craniotomies for different reasons (Krieg et al., 2012). Some studies suggest that melatonin might exhibit acute sleep-promoting effects even in daytime that cannot be solely attributed to the circadian phase shifts, although the topic has raised controversies (see the debate in van den Heuvel et al., 2005*). It has been hypothesized that this effect could be mediated by melatonin's effects on thermoregulation such as increasing heat dissipation. However, this mechanism would be unlikely as bright light exposure can counteract the melatonin-induced thermoregulatory changes without affecting the melatonin-induced sleepiness (Lok et al., 2019). Another hypothesis states that the mechanism might be completely independent of MT_1 and MT_2 receptors and possibly mediated by the binding of melatonin to intracellular receptors (Jan et al., 2011*).

It is likely that MT_1 and MT_2 have different roles in the regulation of REM and non-REM sleep. The knock-out of MT_1 or MT_2 separately results in the decrease of REM or non-REM sleep, respectively. Interestingly, mice lacking both types of receptors do not show altered REM and non-REM sleep (Comai et al., 2013).

Cortisol is another hormone that is under the circadian control. In contrast to melatonin, cortisol levels rise in the second half of the night. Upon awakening, a sharp increase occurs where cortisol levels reach their maximum after 30 to 45 minutes (the cortisol awakening response, CAR). After that, its levels progressively decline. CAR is related to sleep-wake transition and cortisol levels can serve as a marker for arousal. That being said, the exact function of CAR is unclear (Elder et al., 2014*). Importantly, Cuesta et al. (2015) have demonstrated that glucocorticoids act as synchronizers of the circadian clock in human peripheral tissues.

3.5 Chronotypes and the Sleep-Wake Cycle

Chronotype (also diurnal preference) is often generally defined as an individual preference for the timing of daily activities and sleep with respect to the light-dark cycle. That being said, the term has been operationalised in two distinct ways.

Horne and Östberg (1976) developed a 19-item Morningness-Eveningness Questionnaire (MEQ) asking subjects about their timing preferences for their sleeping schedule, exercise, and cognitive performance. Based on self-assessment, a final score is computed based on which the MEQ originally classified subjects into morning types, evening types, or neither. Whilst the composite score is currently used as a continuous trait measure, a recent study suggests the scale to be multidimensional. More specifically, the authors have proposed two distinct (yet correlated) constructs of sleep-pressure build-up sensitivity and dissipation of sleep pressure (Panjeh et al., 2021).

The second method, also based on self-assessment, is the Munich ChronoType Questionnaire (MCTQ). Contrary to the previous method, this questionnaire aims to estimate the midpoint of sleep (also called the mid-sleep point) and sleep duration for workdays and free days. A final score used to assess the person's chronotype is the midpoint of sleep on free days corrected for sleep debt (MSF_{SC}). As such, it conceptualizes chronotype more as a difference between the circadian phase of the sleep-wake cycle and the phase of the light-dark cycle (Roenneberg et al., 2003, 2004). Considering this approach, chronotype can also be assessed using actigraphy. Measures from actigraphy and MCTQ show moderate to high correlations (Santisteban et al., 2018). Scores from MEQ and MCTQ are highly correlated with each other (Zavada et al., 2005).

The distribution of chronotypes in the general population based on MSF_{SC} is near-normal. The mean of the distribution changes with respect to age. During adolescence, the mean value shifts towards later hours. From the early adulthood onward, the average value progressively shifts to earlier hours (Fischer et al., 2017; Sládek et al., 2020). For children between the ages of four and eleven, the Children's ChronoType Questionnaire can be used. It includes adapted versions of both MEQ and MCTQ. The scores also follow a normal distribution (Werner et al., 2009).

As has been implied, an early chronotype is characterised with an earlier sleep onset as well as an earlier waking time compared to a late chronotype. People with late chronotype show greater differences in their sleep timing between workdays and free days (social jet lag) and tend to have larger sleep debt on average (Wittmann et al., 2006). In adolescents, late chronotype corresponds to a worse school performance (Zerbini et al., 2017).

Whilst it has been proposed that DLMO might be used for categorising chronotypes as well, the concordance between DLMO, MEQ and MSF_{sc} derived categories is low and the correlations between the continuous measures are moderate at best. Therefore, DLMO should not be considered a marker of equivalent constructs of chronotype (Reiter et al., 2021).

4 ADHD and its Circadian and Sleep Correlates

4.1 ADHD Symptoms and Aetiology

Attention-Deficit/Hyperactivity Disorder belongs to the class of neurodevelopmental disorders and affects approximately 5 % of children and 2.5 % of adults. It is officially codified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatric Association. Its symptoms can be divided into two domains, the first one being hyperactivity and impulsivity and the second being inattention. Symptoms of hyperactivity/impulsivity may include the inability to sit still, frequent fidgeting, excessive speaking, and impatience. Symptoms classified as inattention can be present as forgetfulness, difficulty listening and following instructions, difficulty in organizing everyday tasks and activities, and others. The diagnostic process takes into consideration the overall number of frequent symptoms and their severity. They negatively impact an individual's everyday functioning in multiple settings and some of them must be present until the age of 12 (American Psychiatric Association, 2013*). Comorbid disorders are common. To illustrate, adults with ADHD are roughly three times more likely to suffer from depression and four times more susceptible to anxiety disorders (Kessler et al., 2006).

Based on the predominance of symptom domains, ADHD is further classified into three clinical presentations: predominantly inattentive, predominantly hyperactive/impulsive, and combined. The term "presentation" was introduced in DSM-5 and was meant to replace the term "subtype" (implying a strictly discrete categorisation) as ADHD symptoms often change across the development. Therefore, the different presentations should be understood as part of a common spectrum (American Psychiatric Association, 2013*). Recently, a new presentation, ADHD-SOM, has been proposed (SOM for *somnus*, meaning "sleep" in Latin) where at least a portion of the symptoms is caused by sleep disturbances and circadian abnormalities, albeit without clearly defined diagnostic criteria (Bijlenga et al., 2019*).

In accordance with its prevalence, it is estimated that ADHD persists in approximately half of the cases into adulthood (Song et al., 2021). Compared to the symptoms of inattention, the symptoms of hyperactivity are more likely to subside in adolescence when measured using the criteria provided by the DSM-5 (Holbrook et al., 2016). Yet, young adults with ADHD exhibit greater risk-taking behaviours (Breyer et al., 2009; Merkel et al., 2016) and report experiencing more inner restlessness than healthy controls (Weyandt et al., 2003).

The cognitive profile of the disorder is highly variable among individuals and a detailed description is beyond the scope of this thesis. Impairments in various types of attention may occur in all ADHD presentations, including the impairments of sustained and divided attention (Tucha et al., 2008). Executive function issues can be present as well, such as those in tasks assessing response inhibition and working memory. Individuals with ADHD also tend to struggle with higher-order executive functions including planning and organization (Pievsky & McGrath, 2018).

The relatively common remission of ADHD in adulthood can be partially explained by the maturation hypothesis. Certain parts of the brain seem to exhibit a lag in maturation compared to healthy controls, with the most prominent delays found in the areas of the prefrontal cortex (PFC) that are involved in executive functions (Shaw et al., 2007). That being said, ADHD seems to be heterogenous in its neurobiology as well.

Many neural pathways have been implied in its pathophysiology. The default mode network activity is associated with mind-wandering, a common symptom of inattention. Studies have demonstrated reduced inhibition of this network during cognitive performance in both children and adults with ADHD. Of special relevance to medication is the dopaminergic reward pathway stemming from the ventral tegmental area and connecting to the PFC. Individuals with ADHD show reduced activation of the striatum when anticipating a reward, whilst there is an increased response in the PFC to reward. This mechanism has been implied to play key roles in impulsivity. Moreover, attention networks are also impaired (Alexander & Farrelly, 2018*).

ADHD aetiology is multifactorial and has a polygenic component. The average heritability estimate of ADHD across studies is 74 % (Faraone & Larsson, 2018). Environmental risk factors involve alcohol consumption and smoking during pregnancy, premature birth and/or low birthweight, brain injury, and possibly prenatal stress. Low support has been found for psychosocial factors such as screen time (Barkley, 2014*).

It has been proposed that ADHD is a continuous trait that can be studied in the normal population as well. In accordance with this approach, studies often look for associations between circadian or sleep changes and ADHD symptoms measured with self-rating or parent-rating scales in otherwise undiagnosed population samples. The validity of such an approach is debatable given that ADHD-like symptoms can co-occur in many other disorders or mental states. DSM-5 requires that the symptoms cannot be explained by another mental disorder and a full diagnosis is also based on the criterium of the age of onset (American Psychiatric Association, 2013*). This thesis will focus mostly on studies of participants with clinically diagnosed ADHD.

4.2 ADHD and the Circadian System

4.2.1 The Associations with Chronotype

ADHD has been consistently shown to be associated with late chronotype in adults. Baird et al. (2012) found that adults with ADHD scored higher on MEQ and that eveningness was strongly correlated with an ADHD index score. Moreover, their melatonin rhythm amplitude was dampened compared to healthy controls. Bumb et al. (2016) confirmed a similar trend in MEQ scores and their association to ADHD symptom severity in a non-medicated sample. A recent meta-analysis concluded that around 30 % of adults with ADHD can be classified as evening types compared to approximately 9 % of them being categorised as morning types (Lugo et al., 2020).

There is also some limited evidence from studies using MCTQ. A small case-control study found that adults with ADHD had a delayed MSF_{SC} by approximately 2 hours on average (Bijlenga et al., 2013b). A larger study involving 202 patients with ADHD and 189 healthy controls found a smaller, yet significant difference in MSF_{sc} of 37 minutes for the category below 30 years old (the results were similar for the category between 30 and 60 years old; Bijlenga et al., 2013a). However, both studies conducted many pairwise comparisons without controlling for the familywise error rate and should therefore be considered exploratory. Also, some of the participants were using ADHD medication.

Spera et al. (2020) examined a sample of 102 adults newly diagnosed with ADHD in an exploratory study. Out of the participants enrolled, 33.3 % fulfilled the DSM-5 criteria for DSPD. The DSPD group was 6 years younger on average and exhibited cannabis use disorder more often. No relation was found between ADHD symptom severity and DSPD. Also, DSPD prevalence was not different among various ADHD presentations. The prevalence of DSPD in the general population is difficult to establish as there may be differences based on sociodemographic variables and the selected diagnostic criteria. That being said, the current estimates are generally lower. A Swedish study used the DSM-5 criteria and estimated the DSPD prevalence to be around 4 % in adolescents and young adults (Danielsson et al., 2016). A New Zealand study found the DSPD prevalence to fall within the range of 1.5 % and 8.9 % depending on the criteria (Paine et al., 2014).

Only a few studies measured chronotype directly in school-age children with ADHD. Durmuş et al. (2017) found higher scores of eveningness compared to healthy controls. This was true when eveningness was measured as a continuous trait but not for the proportion of chronotype categories. Unfortunately, differences between estimated mid-sleep points were not reported. Parent-rated ADHD symptoms were not significantly correlated with eveningness apart from somatic symptoms (which are not ADHD-specific). In children with ADHD, both early and late chronotypes experienced more sleep disturbances than healthy controls of the same chronotypes. Tarakcioglu et al. (2018) did not find any significant differences between children with ADHD and healthy controls in any of the chronotype measures. Children with ADHD scored higher on bedtime resistance and experienced parasomnias and sleep problems more often. That being said, 38.2 % of the ADHD participants were also diagnosed with Oppositional Defiant Disorder (ODD). Another study also failed to find a significant difference in the eveningness scores. The main limitation was the lack of control for ADHD medication and melatonin use (van der Heijden et al., 2018). A pilot study implementing actigraphy did not detect a significant shift in the mid-sleep point of children with ADHD either. The children did not take any ADHD medication during the study (Tonetti et al., 2019). Overall, the evidence suggests that the association between chronotype and ADHD might develop later in life.

4.2.2 Melatonin Profiles in ADHD

In accordance with the delay in MSF_{SC}, the study from Bijlenga et al. (2013b) also found a delayed DLMO in adults with ADHD compared to healthy controls. Moreover, patients with ADHD showed greater time between DLMO and sleep onset and also a delay in the onset of activity. Another study showed that pineal gland volume was strongly and negatively correlated with late chronotype (measured by MEQ) in adults with ADHD, but not in healthy controls. The effect persisted when controlling for age and sex. There was also a strong negative correlation between pineal gland volume and ADHD symptoms. Given that ADHD is associated with decreased brain volume in other areas as well, it is possible that common aetiology underlies these changes. Also, lower pineal gland volume has been associated with insomnia, a commonly reported sleep disturbance in ADHD patients (Bumb et al., 2016).

Research comparing melatonin profiles in ADHD and healthy children is scarce. One study of children with ADHD between the ages of 6 – 12 showed that salivatory melatonin profiles did not differ in their acrophase compared to healthy controls. That being said, when stratified according to age, the children with ADHD between the ages of 10 – 12 had an earlier morning decline in their melatonin levels than controls which suggests that abnormalities in the melatonin profile might also occur progressively with age (Nováková et al., 2011). Nevertheless, circadian changes can be present in children with ADHD and co-morbid sleep disorders. Van der Heijden et al. (2005) found a delayed DLMO by 45 minutes in medication-naïve children with both ADHD and sleep-onset insomnia when compared to children with ADHD only. Studies in adolescents are currently lacking.

4.2.3 ADHD and the Rhythm in Cortisol

Given that patients with ADHD commonly report daytime sleepiness and that arousal dysregulation could be contributing to the disorder, it has been hypothesized that the cortisol rhythm might be impaired in patients with ADHD as well (for more details on the hypothesis, see Ramos-Quiroga et al., 2016).

Studies do not support this hypothesis in non-medicated adults. Hirvikoski et al. (2009) reported that despite the higher perceived stress and post-stress cortisol levels, their diurnal cortisol profile was not different to that of healthy controls. Ramos-Quiroga et al. (2016) corroborated these findings in a study of 109 adults with ADHD and 27 healthy control subjects. No differences in the CAR response were found and the overall results remained the same across different ADHD presentations.

Although some variations of findings in children exist, most studies have detected some differences with respect to morning cortisol profiles compared to healthy controls (Angeli et al., 2018; Chang et al., 2020; Isaksson et al., 2012; Ma et al., 2011). A study of 201 children and adolescents (6 – 17 years old) with ADHD compared to healthy controls showed a dampened CAR and also lower cortisol levels at bedtime. Similarly to the melatonin trend, this effect occurred only in groups of children above the age of ten. No differences were found between the ADHD subtypes, neither were the effects correlated with parent-reported symptom severity. The major limitation of the study was the use of medication. Although there was no significant association with medication use, only a small minority of the ADHD group was not pharmacologically treated, and thus, such comparisons might be underpowered (Isaksson et al., 2012). A recent study of children and adolescents between the ages of 6 – 18 also found lower cortisol levels at bedtime but did not find any differences during awakening. However, differences with respect to the subtypes were reported with participants diagnosed with the combined presentation of ADHD having significantly lower cortisol levels than the inattentive presentation upon awakening and 30 minutes later (Chang et al., 2020). Wang et al. (2011) did not find lower cortisol levels associated with ADHD, but the saliva was sampled at 8 AM only, not with respect to awakening.

Some contradictions arise with respect to comorbidities. Whilst Freitag et al. (2009) reported changes in CAR only in ADHD comorbid with ODD, Angeli et al. (2018) detected lower cortisol levels 30 minutes after awakening in children with ADHD that had no diagnosed comorbidities. Similarly, the study from Isaksson et al. (2012) found that when controlling for ODD, the differences in cortisol levels persisted.

The abnormalities in the cortisol rhythm might reflect a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis in ADHD. Whilst cortisol serves as a marker of HPA activity, salivary α-amylase is a biomarker which reflects changes of a second stress pathway, the sympathetic-adrenal-medullary pathway. The diurnal rhythm in salivary α-amylase opposes that of cortisol. The α-amylase awakening response is characterised by a decline in its concentration. After that, α-amylase levels begin to rise approximately 30 to 60 minutes post awakening (Nater et al., 2007). One of the aforementioned studies examined both the CAR and the α-amylase awakening response in school-age children with ADHD who had no diagnosed comorbidities. In accordance with previous research, the authors found dampened cortisol levels 30 minutes after awakening and lower cortisol levels sampled at 6 PM in comparison with healthy controls. However, no abnormalities in the salivary α-amylase levels were observed. The authors conclude that these results provide evidence for the HPA axis hypoactivity in children with ADHD, but not for alterations of the sympathetic pathway (Angeli et al., 2018).

4.2.4 ADHD and Clock Genes

Given some of the reported changes in the circadian system, it has also been examined if clock gene polymorphisms are associated with ADHD symptomatology. Kissling et al. (2008) were the first to examine a specific single-nucleotide polymorphism (SNP) of the 3' UTR of *CLOCK* in German men with ADHD. Previously, the T allele had been found to be predictive of hyperactive behaviour in animals and of evening preferences. The TT homozygotes scored highest on ADHD severity. A second T allele (CT vs. TT) only predicted higher scores of hyperactivity/impulsivity but not other measures. A subsequent study showed a preferential transmission of the T allele from parents to children diagnosed with ADHD in a Taiwanese sample but not in a sample from the United Kingdom (Xu et al., 2010). In a newer study conducted on a Brazilian sample, the same allele association with ADHD did not reach significance but other ADHD-related *CLOCK* locus SNPs were identified (Carpena et al., 2019).

On contrary, current GWAS have failed to identify any gene variants linked to both chronotype and ADHD. One GWAS has examined the SNPs determining chronotype in relation to ADHD and found no significant association (Lane et al., 2016). Another GWAS failed to detect any SNPs associated with a low relative circadian amplitude being related to ADHD (Ferguson et al., 2018). Similarly, Mota et al. (2020) tested a set of genes associated with circadian rhythmicity and found no relation to ADHD.

The main limits of GWAS include not identifying rare gene variants as well as difficulties in recognizing SNPs when different gene mutations lead to the same phenotype in different individuals. Reverse phenotyping is an approach overcoming some of the limits. Unlike in forward genetics where phenotype is identified first, reverse phenotyping identifies carriers of specific genes and only then is the phenotype characterised. Using such an approach on a Turkish sample, it was found that the *CRY1Δ11* variant linked to a familial form of DSPD was also associated with ADHD. ADHD traits were identified in 46 out of 48 individuals with the mutation, whilst in 44 out of their 48 relatives without the mutation, ADHD was not found either. Most of the individuals were diagnosed with the combined presentation of ADHD. These observations were then cross validated on an Italian sample. Individuals with *CRY1Δ11* were also 15.4 times more likely to have a history of depression (Onat et al., 2020). The *CRY1Δ11* is characterised with an adenine to cytosine transversion in the 5' splice site adjacent to the exon 11. More specifically the mutation occurs in the +3 position, resulting in exon skipping and an in-frame deletion in the C-terminal region. The resulting CRY1Δ11 shows an enhanced nuclear accumulation and binds more readily to its interaction partners, CLOCK and BMAL1. This leads to the displacement of CLOCK and BMAL1 from their target DNA sequences and a subsequent inhibition of these genes (Patke et al., 2017). The authors also found another rare *CRY1* mutation (*CRY1Δ6*) which corresponded with DSPD and ADHD transmission within the family. Authors noted more severe comorbidities in *CRY1Δ6* compared with *CRY1Δ11* carriers. This variant was more stable in comparison with the wild-type form of *CRY1* but its ability to bind CLOCK and BMAL1 was impaired (Onat et al., 2020).

GWAS are also not suitable for identifying gene-environment interactions. Using machine learning, one recent study found SNPs in *PER3* to be among the most predictive candidate genes in combination with parent-reported chronic stress exposure in children. *PER3* polymorphism was also predictive of comorbid conduct disorder that is linked to lower cortisol levels. Given the exploratory nature of the method, these results need further confirmation (van der Meer et al., 2017).

4.2.5 ADHD and Solar Irradiance

The prevalence of ADHD has been linked to solar irradiance (SI, measured as the global horizontal irradiance which is the amount of solar energy per time that reaches the horizontal surface of the Earth). Arns et al. (2013) obtained ADHD prevalence rates across the U.S. from the National Survey of Children's Health in 2003 and 2007. This was estimated based on parent-reported ADHD diagnose rates from randomly selected households. The authors found a non-linear relationship between ADHD prevalence and SI where states having the greatest SI also showed the lowest prevalence rates (Figure 7). The association persisted even when accounting for demographic variables such as Medicaid coverage (a state program providing health coverage to low-income citizens) and gender. Also, the effect was not moderated by seasonal SI changes within the states. Similar results were obtained from Europe where SI explained 57 % of variance in ADHD prevalence in adults, with a limitation being a small sample size of the countries. No relation to SI was found for depression and Asperger syndrome. The associations were also not better explained by altitude or latitude.

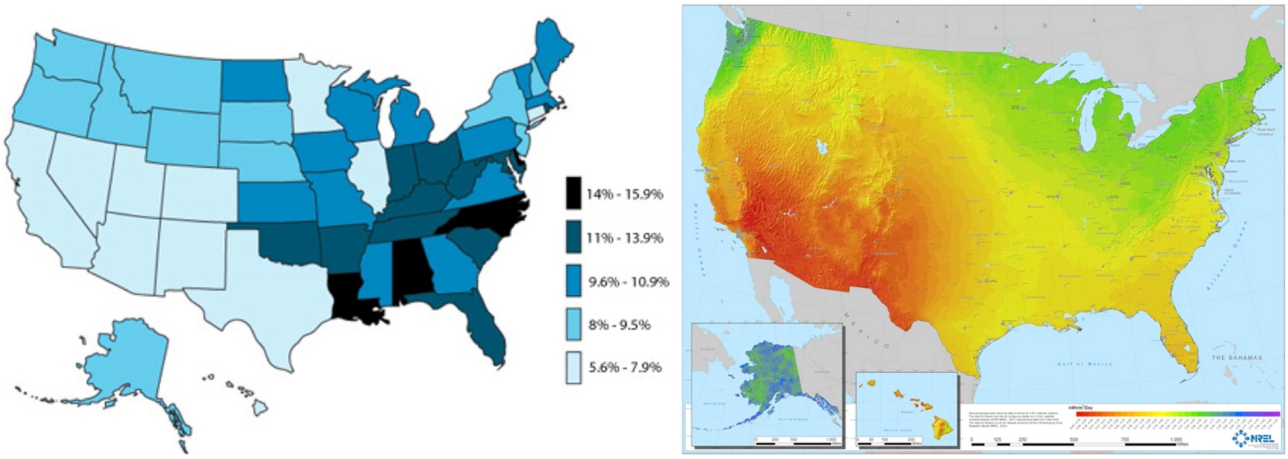

Figure 7: The overlap between ADHD prevalence (left) and solar irradiance (right) in the U.S. Reprinted from Arns et al. (2013, p. 2). Copyright 2013 by Society of Biological Psychiatry. Reprinted with permission.

Hoffman et al. (2014) conducted similar research using prevalence estimates from studies using the DSM-IV criteria. Also, they used local satellite estimates of SI for community samples and estimates based on the SI of the most inhabited areas of the country for national samples. The previously reported relationship was not replicated in their analyses. However, the original authors wrote a response where they showed that aggregating ADHD prevalence rates across years can be problematic. Moreover, a re-analysis of the latter dataset showed that a quadratic term was a better fit for the data, which was subsequently confirmed on the initial dataset. Therefore, it appears that ADHD prevalence rates are lower within the areas of high (California being an example) and low (Scandinavia, UK) SI (Arns et al., 2014). The authors also managed to replicate their analysis on U.S. data from 2011 (Arns et al., 2018).

It remains unclear what explains the observed association. The authors suggest that areas with higher SI might show lower ADHD prevalence because of the phase-shifting effect of light on the circadian system (and therefore counteracting potential interactions between ADHD and late chronotype; Arns et al., 2018). In accordance with this hypothesis, some limited data exist on the effectiveness of light therapy on ADHD symptoms (see the section on chronotherapy). However, this by itself would not account for the quadratic nature of the relationship. One candidate explanation involves polymorphism in the dopamine receptor D4 (*DRD4*) gene that has been associated with ADHD.

In rats, *Drd4* shows the highest expression in the pineal gland and in the retina (approximately 100times more compared to other tissues; Kim et al., 2010). Animal studies have shown that DRD4 plays roles in controlling striatal glutamatergic transmission (Bonaventura et al., 2017), regulating melatonin production (González et al., 2012), and the entrainment of the circadian clock in photoreceptors (Jackson et al., 2011). The 7-repeat variant of DRD4 (DRD4 7R) has been shown to have a reduced ability to inhibit cAMP signalling in ovarian cell lines in comparison with more common DRD4 variants (Asghari et al., 1995). *DRD4 7R* has also been associated with an increased risk of ADHD. However, similarly to the SI-ADHD relation, this was not true for data obtained from Ireland and Norway (Nikolaidis & Gray, 2010). The hypothesis states that high SI might counteract the negative effects of *DRD4 7R*. These effects might be compensated in nations living in low SI areas by some adaptations or other factors such as diet (omega-3 intake from fish; Arns et al., 2018). A preprint (that has not yet been peer reviewed) from Vollebregt et al. (2019) found that in both adults with ADHD and controls, *DRD4 7R* was associated with inattention. However, there was an interaction between the polymorphism and seasonality, showing that individuals with *DRD4 7R* scored lower on inattention when measured during the months of increased daylength. SI was also negatively correlated with symptoms of inattention in *DRD4 7R* individuals only during periods of increasing daylength. The authors concluded that the effects of *DRD4 7R* can be compensated with light exposure. The exact physiological nature of this interaction is yet to be examined.

An alternative explanation of the quadratic SI-ADHD relation hypothesizes the role of vitamin D instead. There is some limited evidence that vitamin D supplements may improve ADHD symptoms in conjunction with methylphenidate pharmacotherapy (Gan et al., 2019). Nations living in high SI areas also have higher plasma concentrations of vitamin D from sunlight exposure. Some of the analysed countries with the lowest solar intensities such as the Nordic regions show adequate amounts of vitamin D due to a higher consumption of oily fish and supplementation (Arns et al., 2018; Lips et al., 2019*).

The potential protective effect of light exposure has also been demonstrated with respect to the *CRY1Δ11* variant. There was a negative correlation between ADHD symptom scores and average daily sunlight exposure in *CRY1Δ11* carriers. No relation was found with respect to mid-sleep points on free days. However, this was not corrected for sleep debt (Onat et al., 2020).

4.3 ADHD and Sleep Disturbances

Studies also show conflicting results with respect to differences in sleep architecture in both children and adults. Given the increasing research interest in the topic, various meta-analyses of the available research have recently been performed. A meta-analysis of 13 studies found that in comparison with controls, adults with ADHD self-reported higher sleep onset latency, worse sleep efficiency and lower sleep quality, more frequent night awakenings, and higher sleepiness during daytime. Only two of these outcomes were confirmed by actigraphy which showed the largest difference in terms of higher sleep latency and worse sleep efficiency. However, the study found no changes in sleep architecture when measured via polysomnography (PSG). Funnel plots did not indicate the presence of publication bias but most studies failed to adequately control for comorbidities (Díaz-Román et al., 2018). A more recent meta-analysis supported these findings. Although the analysis also detected a lower REM density, a significant heterogeneity of studies was present. That being said, PSG also found higher measures of limb movements which is consistent with ADHD having a frequent co-morbidity of the restless leg syndrome (Lugo et al., 2020).

Sleep issues are commonly reported in children with ADHD as well, more specifically by 73.3 % of caregivers (Sung et al., 2008). Nearly half of the PSG studies reviewed by Scarpelli et al. (2019*) reported no differences between ADHD children and controls. A former meta-analysis showed that children with ADHD spent more time in N1 when assessed by PSG. The study found no other differences with either PSG or actigraphy (Díaz-Román et al., 2016). Another meta-study from the same year analysed activity measures from actigraphy and found higher motor activity during the day but no differences in total sleep duration. Secondary analysis also found support for lower sleep efficiency and greater sleep onset latency but high heterogeneity of estimates across studies was reported (de Crescenzo et al., 2016).

It should be mentioned that studies using PSG mostly focused on the macrostructural patterns of sleep. There is some evidence that the reported sleep issues in ADHD patients might reflect changes in sleep microstructure instead. A recent meta-analysis of studies in children and adolescents with ADHD found a lower A1-type CAP rate during N2 in ADHD patients. This is similar to the pattern observed in children with narcolepsy (Biancardi et al., 2021). Interestingly, nonmedicated children and adolescents with ADHD also show reduced serum levels of orexin A (Baykal et al., 2019). Additionally, Takahashi et al. (2020) discovered a genetic overlap between narcolepsy and ADHD symptoms, although ADHD was not clinically diagnosed. In one study, men with narcolepsy were approximately 5 times more likely to have been diagnosed with ADHD in childhood (Ohayon, 2013). The exact nature of the similarities between ADHD and narcolepsy are yet to be explored by further research.

The meta-analysis of the sleep microarchitecture also identified an age-dependent difference in the slow-wave activity (SWA)[4]. Analyses controlling for covariates (including medication use) showed higher amounts of SWA in children prior to the age of 10 and lower amounts of SWA above. The authors suggest that the observed changes in SWA are likely to be related to the development of synaptic density in ADHD. In general,

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[4] Whilst SWS is a term reserved for N3, SWA refers to the microarchitectural measures of delta activity irrespective of the sleep stage. SWA corresponds to the delta activity within the range of 0.5 and 4.5 Hz.

the pattern of topographical SWA distribution reflects cortical maturation. SWA in central regions also decreases in adolescence due to synaptic pruning, a process that is known to be disrupted in various neuropsychiatric disorders (Biancardi et al., 2021). Animal research has found another potential source of the abnormalities in the locus coeruleus (LC). Class IB phosphoinositide 3-kinase (PI3Kγ) is an enzyme highly present in the noradrenergic neurons of LC. PI3Kγ is part of a phosphodiesterase 4D (PDE4D) regulating complex. *PI3Kγ* knockout in mice LC results in a decreased PDE4D activity, which in turn leads to a cAMP-mediated enhancement of CREB signalling. Subsequently, LC projection areas show increased levels of noradrenaline compared to dopamine. This is associated with an ADHD-like phenotype performing worse on attention tasks and showing signs of hyperactivity (D'Andrea et al., 2015). Moreover, a recent optogenetic study has shown that the stimulation of LC neurons during sleep in rats resulted in a decrease in SWA but not in changes in the sleep macrostructure. The reduction in SWA correlated with errors made in a hippocampal learning memory task (Swift et al., 2018). More research is needed to clarify if similar changes in LC are present in humans with ADHD and whether they might be related to the sleep disturbances.

Longitudinal studies might provide more insight with respect to the development of ADHD, sleep issues, and their mutual relations. The Environmental Risk Longitudinal Twin Study followed 1,116 twins from England and Wales at the ages of 5, 7, 10, 12, and 18 years. Sleep variables were measured using the Pittsburgh Sleep Quality Index. The analysis showed that ADHD remission also corresponded with the remission in higher rates of sleep disturbances, as the diagnosis of ADHD in childhood did not predict sleep quality when adjusted for having an ADHD diagnosis in adulthood. The results persisted even when controlling for comorbidities, excluding participants taking ADHD medication, and analysing the associations between sleep quality and inattentive or hyperactive/impulse symptoms separately. Using data from monozygotic and dizygotic twins, genetic influences were estimated to explain 55 % of the estimated phenotypic correlation between ADHD and sleep quality, whilst the nonshared environmental influences explained 45 % of the correlation (Gregory et al., 2017).

Sleep disturbances may also worsen ADHD symptoms as demonstrated by a few studies on sleep restriction and extension. Gruber et al. (2011) conducted an experiment in children with ADHD and healthy controls between the ages of 7 and 11. A sleep restriction of 1 hour for 6 days resulted in a worse performance in both groups on a continuous performance test (CPT). Furthermore, compared to a baseline condition, CPT scores of inattention reached their respective cut-off score for clinical significance in ADHD children following the sleep restriction condition. A study of a similar design but with sleep extension instead of sleep restriction showed that when the bedtime of children with ADHD was shifted earlier by 90 minutes (PSG showed an extension of sleep by 52 minutes on average), their performance on an inhibitory control test increased by 13 %. Sleep extension did not improve the performance of the healthy control group (Cremone-Caira et al., 2020). Similar studies in adults with ADHD are yet to be conducted.

Understanding the complex interplay between sleep issues, circadian abnormalities and ADHD might require studying their interactions through health-related behaviours. One study found that adolescents with ADHD spend significantly more time using electronic devices before sleep compared to healthy controls. Moreover, reported sleep problems were associated with late chronotype (Budagova & Bahadir, 2019).

Another study also found greater screen time in children and adolescents with ADHD and showed that higher use of electronic devices correlated with deviation from individual sleep requirements (Thoma et al., 2020). Patients with ADHD struggle with delaying reward and are more susceptible to internet addiction (Wang et al., 2017). Although the exact causal pathways are yet to be examined, it is likely that media use and struggles with maintaining sleep hygiene might result in later bedtime, sleep restriction, and a subsequent worsening of the symptoms. This could also possibly explain why some of the studies show different results in children with ADHD.

4.4 Chronotherapy and Sleep-Focused Interventions for ADHD

Some research has also examined if chronotherapy (that is, light therapy and melatonin administration) and/or sleep-focused interventions improve ADHD symptoms. Such research might indicate if ADHD severity is indeed causally intertwined with sleep issues and circadian abnormalities.

4.4.1 Chronotherapy of ADHD

Light therapy is often used for the treatment of seasonal affective disorder, a mood disorder characterised with seasonal episodes of depression during winter months, and circadian sleep disorders such as DSPD. Most commonly, a full-spectrum light source (bright light therapy, BLT) of a defined light intensity is used (usually 10,000 lux at a known distance). Patients are asked to sit near the light source at a required distance so that the light reaches the eyes. In order to benefit from the phase-advancing effects of light, this is often performed after awakening for 30 minutes. Nevertheless, the exact use depends on the condition treated as well as other factors. Commercial light therapy boxes are also available (for example, see the procedure described in Fargason et al., 2017).

So far, only one small study has evaluated the effectiveness of a standalone BLT with respect to ADHD symptoms. A 3-week-long trial taking place in autumn and winter used BLT in 29 adults with ADHD. Measures of chronotype, ADHD symptoms, cognitive performance, and depression were obtained pre and post intervention. There was a significant shift towards morningness by 5 points on average on the MEQ scale. Moderate improvements were found in most of the measured ADHD symptoms and some of the objective attention and executive function test measures. Improvements in CPT were correlated with the phase-shift towards morningness in MEQ. However, the study had some important weaknesses. First and foremost, no control group was recruited. Second, 12 individuals had a comorbid depression. Whilst 4 individuals had seasonal affective disorder, the results were confirmed even after their exclusion from a subsequent analysis. Also, seasonality did not predict the observed improvements (Rybak et al., 2006).

More recently, a pilot study combined morning BLT and the use of blue light filtering glasses in late afternoon for two weeks in 16 adults with ADHD. It found similar results with actigraphy measures and DLMO, albeit with similar design limitations. More specifically, participants had a significantly earlier DLMO by 31 minutes and an earlier mid-sleep point by 57 minutes post intervention compared to their baselines. These changes were also associated with improved self-reported ADHD symptoms for both inattention and hyperactivity/impulsivity. Although not reaching statistical significance, the study also showed trends for an earlier sleep start and sleep end. Sleep quality was measured using a sleep quality index, sleep diaries, and actigraphy indicators. The self-report measures found improvements in daytime sleepiness and overall sleep quality. Similarly to the studies outlined in the section on sleep, there was a discrepancy in the subjective and objective measures, as actigraphy did not find an increase in sleep efficiency but did find a statistically nonsignificant increase in sleep fragmentation (Fargason et al., 2017).

Some research has also focused on melatonin use. A 4-week randomised-controlled trial allocated 105 children (6 – 12 years) with both ADHD and sleep onset insomnia to either a placebo condition or a melatonin condition. The randomisation process was stratified with respect to comorbidities. The participants were not taking ADHD medications and did not have a history of melatonin use. The melatonin dose was based on body weight (3 or 6 mg) and the tablets were administered once daily at 7 PM. Specific bedtime was not required. Improvements have been detected in all primary actigraphy measures. Melatonin advanced sleep onset by 27 minutes on average (compared to a 10-minute delay in the placebo group) and decreased sleep latency by 21 minutes (compared to 3 minutes). Other improvements in actigraphy measures were the increase in the total time spent asleep and a greater sleep efficiency. Accordingly, DLMO was advanced by 44 minutes on average (compared to a 13-minute delay in the placebo condition) and baseline DLMO predicted greater phase-advances following the melatonin intervention. Importantly, no significant differences between the melatonin and placebo groups were observed for changes in cognitive testing (interference control and sustained attention). Also, no significant improvements in quality of life were detected (van der Heijden et al., 2007). After the trial, parents of all the children were offered to continue the use of melatonin (or start when the child was allocated to the placebo group). A few years later, follow up questionnaires were obtained. 65 % of the follow up parents reported continuing the use of melatonin use every day. In 88 % of the children, they found it to be an effective treatment for the child's sleep onset issues and 70.8 % reported improvements in the child's behaviour during the day (Hoebert et al., 2009).

Recently, one trial randomised 51 adults with both ADHD and DSPD into one of three conditions: placebo, melatonin, or melatonin and BLT. 0.5 mg of melatonin or placebo was taken once daily. Melatonin was administered three hours before the individual DLMO, then four hours prior to the initial DLMO in the second week and five hours in advance in the third week. BLT was used in the morning (between 7 to 8 AM) for half an hour. The placebo and melatonin conditions were double blinded. However, the condition where melatonin was used in combination with BLT was known to both the researchers and the participants. Similarly to the previous research, participants were not taking ADHD medication, additional melatonin, or other sleep medications. Additionally, the participants also received sleep education (such as avoiding blue light from electronic devices at bedtime). Measures were obtained at baseline, post-intervention (the day after the third week), and 2 weeks later (with the discontinuation of all treatments). Post-intervention, melatonin showed a significant phase-advancement effect compared to placebo by shifting the average DLMO by 1 hour and 28 minutes. Self-reported ADHD symptoms improved by 12 %. 2 weeks after treatment discontinuation, both DLMO and ADHD symptoms returned to their baseline levels. The melatonin + BLT group advances in DLMO did not significantly differ from the melatonin-only group. Interestingly, the combination group did not achieve improvements in ADHD symptoms above the levels of the placebo group. Importantly, DLMO advancements did not mediate the improvements in ADHD symptoms (van Andel et al., 2021).

In summary, melatonin treatment does help the associated DSPD or sleep-onset insomnia in patients with ADHD. However, results are mixed with respect to the alleviation of ADHD symptoms. The differences in the presented results might arise due to differences in methodology (dosing, duration, sleep education as part of the design etc.). That being said, the fact that melatonin use does show improvements in ADHD symptoms in adults and not in non-medicated children might be consistent with previous findings showing that some circadian abnormalities have been identified in children above the ages of 10. Nevertheless, as the improvements in adults were not mediated by the DLMO shifts, it is unclear what other mediators might explain the observed benefits of the melatonin treatment. More research is needed with respect to the effects of light therapy.

4.4.2 Sleep-Focused Interventions and ADHD symptoms

Some studies also focused on complex sleep interventions. Before the evidence is reviewed, it should be emphasized that especially for sleep research, findings in patients using ADHD medication might not always generalise to the non-medicated ADHD population. For instance, methylphenidate, the most commonly used ADHD medicine, has been associated with insomnia as a side effect. Moreover, the effects of ADHD medication on sleep in ADHD populations are complex and beyond the scope of the thesis (as an example, see Becker et al., 2016).

Hiscock et al. (2015) randomly assigned children with ADHD to either receive 3 sessions of individualised sleep intervention (using behavioural techniques and educating the parents on sleep hygiene) from a psychologist or a trained paediatrician, or to attend regular check-ups as the control group. The intervention group showed a moderate reduction in parent-reported ADHD symptoms at a 3 and 6 month follow up. Moreover, a mediation analysis showed that approximately 50 % of the parent-reported improvement in ADHD symptoms was mediated by the reduction in parent-reported sleep disturbances at the 3-month assessment and a 33% mediation was shown at the 6-month follow up. More recently, the same team conducted another randomised-controlled trial using the same intervention in 244 children with ADHD and sleep disorders. The improvements in parent-reported ADHD symptoms were maintained at a 12month follow up. The intervention showed greater efficacy for children taking medication at the start of the study, suggesting the importance of accounting for the role of medication when examining the effects of sleep interventions on ADHD symptoms (Sciberras et al., 2020).

Unfortunately, such randomised-controlled trials in adolescents and adults with ADHD are missing. In one study, 19 adults with ADHD and sleep issues underwent 10 weeks of cognitive behavioural therapy for insomnia adjusted for ADHD. All of the self-reported ADHD symptoms were reduced post-intervention and the benefits were maintained at a 3-month follow up. The greatest improvements were noted on the hyperactivity subscale where the average score dropped below the clinical cut-off score. However, no conclusions about causality can be drawn given the lack of a control group. Similarly to the studies in children, most patients were taking ADHD medication (Jernelöv et al., 2019).

All things considered, there is some promising evidence that correcting sleep issues in ADHD patients might improve ADHD symptoms, especially in children. That being said, more research using objective sleep measures as well as considering the effects of ADHD medication is needed.

5 Conclusions

Circadian abnormalities and sleep issues are commonly present in children, adolescents, as well as in adults with ADHD. Nevertheless, given that patients with ADHD are heterogenous in behaviour and cognitive measures, it is not surprising that studies often show conflicting results and that findings tend to be highly variable among individuals.

Studies of circadian correlates in adult patients with ADHD reached different conclusions compared to studies of children with ADHD. However, the following summary should be approached with caution as study methodologies might not always be comparable. Most studies agree that ADHD in adults is associated with late chronotype. Similarly, adults with ADHD show a higher prevalence of clinically diagnosed DSPD (estimated to be 33 %) and a delayed DLMO. In contrast, studies in children yield more mixed results. There is little evidence for the association between ADHD and chronotype in children but unlike in adults, a dampened CAR seems to be present.

Sleep issues are consistently reported by the majority of ADHD adults and caregivers of children with ADHD. However, more objective measures (actigraphy and PSG-assessed sleep macroarchitecture) confirmed only a few of the reports compared to healthy controls, such as higher sleep-onset latency and sleep efficiency. New research suggests that sleep disturbances might reflect changes in sleep microarchitecture, a set of PSG measures not examined in most of the previous studies. Indeed, children with ADHD show abnormal CAP and SWA profiles.

Interestingly, a similar pattern exists across studies in children. When stratified according to age, some circadian measure changes (melatonin profiles, CAR) were only found in participants that were 10 years and older. Also, while children below the age of 10 have higher SWA, this changes to a lower SWA when older. These results may reflect an important developmental milestone. Although the developmental lag of cortical thickness and possibly changes in synaptic pruning are promising candidates for the underlying cause, the potential role of health-related behaviours such as increased screen time should also be considered. Additionally, ADHD remission in adulthood is associated with the remission of sleep disturbances, showing that more longitudinal research might be necessary to understand the interactions between ADHD, sleep, and the circadian system.

As has already been mentioned, it has been proposed that circadian and sleep disturbances play a key role in ADHD aetiology, or even that ADHD might be a circadian disorder. Recently, rare gene variants linked to both DSPD and ADHD have been discovered. Furthermore, there is a significant genetic overlap between ADHD and sleep issues. Experiments in children have shown that sleep restriction results in the worsening of ADHD symptoms and sleep extension in their improvement. Also, considering that light is the main zeitgeber of the central clock, lower ADHD prevalence in the areas of high SI might be explained with some aetiological similarities of circadian disruption and ADHD.

Unfortunately, most of the research is correlational and direct evidence is missing. ADHD is a multifactorial disorder and the aforementioned genetic variants are rarer. On top of that, the direction of causality can be difficult to establish. Randomised-controlled trials using chronotherapy and sleep interventions that also monitor changes in ADHD symptoms might provide some important answers in the future. Whilst showing promising results, the sample sizes, methodologies, and studied populations are heterogenous and often limited.

There are also important limits to the thesis itself. Firstly, apart from the few exceptions, only studies of clinically diagnosed ADHD patients were considered for the reasons mentioned. That being said, it is also possible that some important connections that have not yet been confirmed on formally diagnosed samples have been neglected as a result. Secondly, the thesis did not focus on ADHD medications as a separate issue as its main goal was to review the circadian and sleep correlates of ADHD itself. Yet medication was one of the most common confounders and might also advance the current scientific understanding of physiological overlaps. Thirdly, little attention has been dedicated to differences among ADHD presentations as studies tend to be highly inconsistent on this issue, possibly due to commonly small sample sizes not allowing for such stratification.

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