ADHD 24/7: Circadian Clock Genes, Chronotherapy and Sleep/Wake Cycle Insufficiencies in ADHD

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Abbreviations:

ADHD:	Attention-Deficit Hyperactivity Disorder,
BL:	Bright Light,
DSPD:	Delayed Sleep Phase Disorder,
DLMO:	Dim Light Melatonin Onset,
DSWPP:	Delayed Sleep-Wake Phase Disorder,
EEG:	Electroencephalogram,
ipRGCs:	Intrinsically Photosensitive Retinal Ganglion Cells,
LT:	Light Therapy,
N24SWD:	Non 24 hour Sleep-Wake Rhythm Disorder,
SAD:	Seasonal Affective Disorder,
SCN:	Suprachiasmatic Nucleus,
SOI:	Sleep Onset Insomnia,
SWD:	Shift Work Disorder

Abstract:

Objectives. The current paper addresses the evidence for circadian clock characteristics associated with Attention-Deficit Hyperactivity Disorder (ADHD), and possible therapeutic approaches based on chronomodulation through bright light therapy. *Methods.* We review the data reported in ADHD on genetic risk factors for phase-delayed circadian rhythms and on the role of photic input in circadian re-alignment. *Results.* Single nucleotide polymorphisms (SNPs) in circadian genes were recently associated with core ADHD symptoms, increased evening-orientation and frequent sleep problems. Additionally, alterations in exposure and response to photic input may underlie circadian problems in ADHD. Bright light (BL) therapy was shown to be effective for re-alignment of circadian physiology toward morningness, reducing sleep disturbances and bringing overall improvement in ADHD symptoms. The susceptibility of the circadian system to phase shift by timed BL exposure may have broad cost-effective potential implications for the treatment of ADHD. *Conclusions.* We conclude that further research of circadian function in ADHD should focus on detection of genetic markers (e.g., using human skin fibroblasts) and development of BL-based therapeutic interventions.

Introduction

There is a substantial literature linking dysfunction of the circadian timing system to the etiology and/or symptomatology of common neuropsychiatric disorders (Foster et al., 2013). Such evidence includes the use of *ex vitro* models for the monitoring of circadian rhythms in gene expression (Brown et al., 2005; Hida et al., 2017), behavioral monitoring through the use of actigraphy (Ancoli-Israel et al., 2003) and the assessment of other physiological, endocrine and psychological rhythmic processes (Refinetti, Lissen, & Halberg, 2007). The relevance of the circadian system to neuropsychiatric disorders is further supported by genetic association studies (Kalman, Garbett, Janka, & Mirnics, 2016). One such disorder is Attention Deficit Hyperactivity Disorder (ADHD).

Attention-deficit hyperactivity disorder (ADHD) is a neuropsychiatric condition characterized by inattention and/or hyperactivity-impulsivity that interferes with everyday functioning (Douglas, 1999; Kaiser, Schoemaker, Albaret, & Geuze, 2014). Based on the prevailing symptomatology, ADHD has three presentations: (i) predominantly inattentive -, (ii) predominantly hyperactive– impulsive -, and (iii) combined –(Gaub & Carlson, 1997). ADHD, although a childhood-onset neurodevelopmental condition, is nevertheless a frequent and disabling condition in adults (Magnin & Maurs, 2017) due to the relatively high persistence rates of 40-50% (Lara et al. 2009). The prevalence of ADHD is around 5.3-7% for children and adolescence, and 3.4-4.4% for adults (Polanczyk et al. 2007, Fayyad et al. 2007, Polanczyk and Rohde 2007). Although the etiology of ADHD remains poorly understood, ADHD in all age groups has a strong genetic component (Franke et al., 2011).

While attention problems are recognized as a core deficit (Douglas, 1999), deficits in executive functions (e.g., planning, inhibition and set-shifting) (Pennington & Ozonoff, 1996), motor functioning (Adi-Japha, Fox, & Karni, 2011; Goulardins, Marques, & De Oliveira, 2017; Kaiser, et al., 2014; Mostofsky et al., 2006), skill learning ("how to" memory)

(Adi-Japha, et al., 2011; Korman, Levy, & Karni, 2017; Mostofsky, et al., 2006; Nicolson & Fawcett, 2007), emotional instability (Petrovic & Castellanos, 2016) and sleep problems (Philipsen, Hornyak, & Riemann, 2006) are recognized as additional key characteristics.

The symptomatology of ADHD may be positively influenced by shifting misaligned circadian rhythms to more appropriate phase, through pharmacological or behavioural interventions (Mayer et al., 2018). A successful therapy to influence the circadian rhythm via changes in the expression of relevant genes, for example, in seasonal depression, is bright light (BL) therapy, and thus it might be useful for the treatment of ADHD (Kaladchibachi & Fernandez, 2018; Pail et al., 2011). A recent position paper of physicians and researchers from the EU has addressed the need to explore and develop light based interventions to ameliorate ADHD (Coogan, Baird, Popa-Wagner, & Thome, 2016).

Neurophysiological underpinnings of behavioural manifestations of the ADHD were linked to brain structures such as the dorsal lateral prefrontal cortex, ventral lateral prefrontal cortex, insula, anterior cingulate, and dysfunction of dopaminergic systems (Sowell et al., 2003; Tripp & Wickens, 2008). Stimulants, such as methylphenidate, and atomoxetine are currently the most common pharmacological treatments for ADHD (Chan, Fogler, & Hammerness, 2016). Appropriate doses of stimulants increasing dopamine's availability effectively improve attention, decrease hyperactivity, increase behaviour management and improve executive functions in individuals with ADHD (Advokat, 2010; Arnsten, 2006; Rubia et al., 2014; Spencer et al., 2013). Serious adverse events are very rare, but a high proportion, up to 50%, of stimulant users suffers a range of non-serious adverse events, which may explain the relatively high withdrawal rates (6-17%) (Storebo et al., 2018). Moreover, some patients are unresponsive to stimulant medications. Most common non serious short-term and long-term adverse effects include insomnia and other sleep problems, headache, abdominal pain and poor appetite (Graham & Coghill, 2008; Storebo, et al., 2018).

Non-stimulants, such as atomoxetine may affect cardiovascular parameters, but do not affect sleep (Graham & Coghill, 2008). These recently reported numbers call to investigate what is the cost of such "non-serious" but chronic sleep problems and meal mis-timings due to medications. How these problems are related to the inherent, treatment independent problems with sleep and late chronotype in significant proportion of ADHD patients across the lifespan (Coogan & McGowan, 2017)?

In the current review we aim underscore the importance of continuing the search for biological markers of ADHD and incorporation of non-pharmacological modalities in treatment protocols utilizing chronobiological perspective on ADHD etiology. We hypothesize that patients with ADHD are candidates for a novel clinical approach that includes a confirmatory laboratory evaluation, incorporating clock gene-based diagnosis and circadian behavioural and biomarker's testing. We propose that the use of Light Therapy (LT) has a potential to induce short-term and long-term improvements in cognitive, behavioural and emotional measures in patients with ADHD. Our review suggests a potential directive in encouraging research to 1) determine the benefits of coupling fibroblasts' genes expression phase markers with cognitive (e.g., reaction time) and physiological markers (e.g., melatonin, cortisol) as a multi-dimensional diagnostic method of circadian dysregulation in ADHD; 2) evaluating whether appropriately timed LT is a potent sleep, cognitive and emotional enhancer in ADHD, either directly or mediated via circadian phase shifting. In particular, of interest are the differential effects of three principally different light protocols (natural light, blue light and dawn-like gradually changing light) on the short- and long-term cognitive and emotional functional outcomes; and 3) evaluating, through randomized, placebo-controlled studies, the relative effectiveness of light therapy compared to standard pharmacological therapy to treat ADHD symptoms. We conclude that LT interventions that independently or in conjunction with pharmacological treatment may improve core

144 symptomatology of ADHD or compensate for common adverse effect of stimulant
145 medications, primarily, sleep insufficiency, is of highest clinical importance. Moreover, LT
146 has the potential for augmentation or even prevention of psychiatric comorbidities in adult
147 ADHD, such as sleep and mood disorders.

148 The review starts with an overview of sleep and circadian rhythm dysfunction in
149 ADHD. Next, we describe the maintenance of the circadian timekeeping system "by" clock
150 genes, and its modulation by photic input. Recent findings unveiling the connection between
151 the circadian function and clock genes in different psychiatric disorders and in ADHD,
152 including the fibroblasts model, are summarized in the core part of the paper. In the
153 concluding section, light therapy for circadian alignment in ADHD and future directions of
154 integrated research, diagnosis and treatment are discussed.

155 **ADHD, sleep and circadian rhythm dysfunction**

156 ADHD in adolescents and adults is associated with the evening chronotype (Baird,
157 Coogan, Siddiqui, Donev, & Thome, 2012; Bumb et al., 2016; Coogan & McGowan, 2017;
158 Vogel et al., 2017), with ADHD individuals displaying preference for late sleep timing and,
159 accordingly, late timing of awakening. While more than 40% of adults with ADHD display
160 an evening preference, only about 11% of age-matched healthy peers show this preference
161 (Rybak, McNeely, Mackenzie, Jain, & Levitan, 2007). Greater eveningness is associated with
162 shorter night sleep periods. Consequently, a sleep debt may play a causal role in the core
163 symptoms of inattention and increased impulsivity (Rybak, et al., 2007). The hyperactivity of
164 ADHD patients is expressed in greater motility at night-time and may lead to sleep
165 deprivation (Philipsen, 2006). Also, seasonal affective disorder (SAD), a type of depression
166 disorder directly linked to circadian disruption, shows high comorbidity with ADHD
167 (Wynchank et al., 2016). The core symptoms of ADHD, such as inattention, impulsivity and
168 impatience, are typical outcomes of sleep deprivation even in typical adults (Corkum,

Tannock, & Moldofsky, 1998). As many as 70% of children and up to 83% of adults with ADHD have been reported as having sleep problems (Philipsen, et al., 2006) with sleep onset insomnia (SOI) being the most common problem (Van der Heijden, Smits, Van Someren, & Gunning, 2005). Adults with ADHD also report reduced sleep quality, meaning difficulties in falling asleep and in waking up (Kooij & Bijlenga, 2013). More than 60% of adults with ADHD report increased sleepiness during day-time (Kooij & Bijlenga, 2013; Van der Heijden, et al., 2005; Van Veen, Kooij, Boonstra, Gordijn, & Van Someren, 2010). Interestingly, neurobiological delayed timing of melatonin secretion is found in children and adults with ADHD (Van der Heijden, et al., 2005; Van Veen, et al., 2010). Sleep problems and ADHD seem to interact in a complex bidirectional manner with sleep disturbances exacerbating ADHD symptoms and ADHD symptoms exacerbating sleep disturbances (Owens et al., 2013). In normally developed adults, sleep after practicing a new motor skill, supports memory consolidation processes, contributing to the generation of stable, enhanced and long lasting procedural memory representations (Debas et al., 2010; Korman, Raz, Flash, & Karni, 2003), but when applying the protocols developed for normally developed controls to adults with ADHD, overnight motor memory consolidation is hampered (Adi-Japha, et al., 2011; Fox, Karni, & Adi-Japha, 2016; Korman, et al., 2017).

ADHD is also associated with disrupted regulation of arousal during wake (Brennan & Arnsten, 2008; Hegerl & Hensch, 2014). Arousal is the physiological and psychological state of being awoken or of sense organs stimulated to a point of perception (Schachter, 1964). Individuals with ADHD tend to be under-aroused in “normal” performance and learning conditions (James, Cheung, Rijsdijk, Asherson, & Kuntsi, 2016; Wainstein et al., 2017; Zentall & Zentall, 1983). An optimal arousal level is considered a prerequisite for successful cognition functioning (Yerkes & Dodson, 1908; Zentall & Zentall, 1983). Cognitive theories of ADHD, such as the state regulation model (van der Meere, 2005) and

dual-process models (Halperin & Schulz, 2006; Johnson et al., 2007) propose that the high within-subject fluctuations of cognitive performance in ADHD may reflect problems in regulating arousal. Unstable and low arousal results in the inability or difficulty to sustain attention on any task of waning novelty (Sikstrom & Soderlund, 2007; Strauss et al., 2018). Resting EEG parameters of arousal level (Strauss, et al., 2018) and arousal stability (Sander, Arns, Olbrich, & Hegerl, 2010; Strauss, et al., 2018) were recently suggested as biomarkers for adult and paediatric ADHD. The restless behaviour of individuals with ADHD during wake is interpreted as self-stimulation in order to raise their arousal level (Baijot et al., 2016; Strauss, et al., 2018) and, consequently, performance. Altogether, altered circadian functioning is associated with ADHD (Coogan & McGowan, 2017), suggesting that inner, biological time-keeping malfunction may be an important factor in this clinical condition.

The circadian timekeeping system is generated by "clock" genes

The circadian timekeeping system underpins the generation of near 24-hour rhythms of variations in physiology and behavior. These cycles are not a response to the changes in the light or temperature around us: they are genetically encoded in a cell-autonomous manner, and at a systems level the circadian timekeeping is the result of a hierarchical, highly distributed whole organism system (Albrecht, 2012). The circadian clock cycle continues running, in the absence of periodic environmental stimuli, to best synchronize physiology and behavior, and with reference to the external environment, to the earth's rotation (Duffy, Rimmer, & Czeisler, 2001). However, the circadian clock can only reliably fulfil its function in a constantly changing environment if it is synchronized ("entrained") to appropriate temporal cues in the environment. For mammals, the most important entraining stimulus ("zeitgeber") is light (Hughes, Jagannath, Hankins, Foster, & Peirson, 2015). Other non-photic day time events, such as meal timing and social cues may also serve as zeitgebers,

although under normal circumstances light is setting circadian phase (Roenneberg & Merrow, 2016).

The master circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore, 1997; Reppert & Weaver, 2002). The SCN comprises a cell-autonomous oscillatory network of synchronized individual clock neurons, which projects its rhythm onto cell-autonomous clocks throughout the brain and peripheral tissues (Welsh, Takahashi, & Kay, 2010). A subset of SCN neurons are stimulated by photic input transmitted via the retinohypothalamic tract. The retinal receptors (intrinsically photosensitive retinal ganglion cells (ipRGCs)) are specialized cells independent of the visual system. The signal is monosynaptical propagated using glutamate as a transmitter. This results in activation of the retinal receptors through modulating the electrophysiological properties. (Welsh, et al., 2010). Moreover, SCN neurones display circadian rhythms in their electrophysiological properties, and these electrophysiological rhythms are underpinned by circadian clock genes (Belle, Diekman, Forger, & Piggins, 2009). At the molecular level, circadian rhythms are generated via feedback loops involving a panel of clock genes and their protein products (Albrecht, 2012).

At the molecular level, circadian rhythms are generated via feedback loops involving a panel of clock genes and their protein products (Albrecht, 2012). The most important circadian genes include circadian-locomotor output-cycle kaput-genes (Clock), brain and muscle-Arnt-like 1 gene (Bmal1), periodic homolog genes (Per1/2/3) and cryptochrome genes (Cry1/2) (Sato et al., 2006). The transcription factors CLOCK and BMAL1 heterodimerize and consequently bind to the promotor region of PER and CRY resulting in activation of these genes. After translation and transcription, PER and CRY proteins are gradually stabilized during the day and inhibit the activity of CLOCK and BMAL1. The result of this negative feedback loop is the inhibition in the expression of PER and CRY (Lee,

Etchegaray, Cagampang, Loudon, & Reppert, 2001; Shearman et al., 2000). After 24 hours one cycle is finished and the process starts again. CLOCK and BMAL1 are not only involved in the activation of PER and CRY. Both activate clock-controlled genes in different peripheral tissues (Janich et al., 2011; Marcheva et al., 2010; Paschos et al., 2012). This circadian clock gene cycle has a widespread influence on the transcriptome, with 40% of all mammalian genes showing circadian rhythms in their expression in at least one tissue (Zhang, Lahens, Ballance, Hughes, & Hogenesch, 2014).

The SCN is rather a "master synchronizer" than a pacemaker. Most tissues show circadian patterns of gene expression when cultured, although such rhythms dampen over a number of days (Buhr & Takahashi, 2013). The SCN communicates with peripheral clocks over several pathways, including hormonal cues (glucocorticoids, melatonin) and indirect cues (body temperature, food intake; (Panda, 2016)). Each cue can phase-shift a peripheral oscillator but may not alter the phase of the central clock, potentially leading to an internal desynchrony of the circadian system, which in turn may lead to adverse outcomes (Roenneberg & Merrow, 2016).

Chronotype, Clock genes and ADHD

One interesting pivot-point for the examination of genetic factors that may link ADHD and circadian clocks is chronotype. Chronotype is usually measured as the manifestation of preferred or actual timing of sleep/wake behaviour, and is shaped by ontological, environmental and genetic factors (Adan et al, 2013). Later chronotype (eveningness) is characterised by a later phase of entrainment of the endogenous circadian system to environmental time cues resulting in later self-selected timing of sleep onsets and offset, and morning types display an earlier phase of entrainment and converse effects on sleep timing (Roenneberg et al, 2003). Chronotype may also be shaped by inter-individual differences in sleep homeostasis, and as such should not be viewed as a purely circadian

phenomenon (Mongrain et al, 2006). Later chronotype is associated with a number of psychopathological features in both clinical and non-clinical populations (Antypa et al, 2017; Lemoine et al, 2017; Hsu et al, 2012). Chronotype has also been shown to influence a broad range of cognitive functions, including the ADHD-relevant domains of attention (eveningness associated with more inattention; Hennig et al, 2017) and impulsivity and risk-taking (eveningness associated with more impulsive behaviours; McGowan et al, 2016; Ponzi et al, 2014). The relative advantage of assessing chronotype over other circadian parameters is that it can be reliably measured using validated questionnaires, and as such is more scaleable than other approaches such as actigraphy or physiological and molecular measures (Adan et al, 2012).

As mentioned previously, ADHD is associated with late chronotype, possibly indicating a later entrained phase of the clock, altered sleep homeostasis, or an interaction between the two (Coogan & McGowan, 2017). Similar to other behavioural traits, chronotype is found be to be heritable, with reported rates of heritability from family and twin-studies in the range of 21% (Evans et al, 2011) to 40-50% (von Schantz et al, 2015; Barclay et al, 2010). The putative genetic basis of chronotype has recently been explored in a number of genome-wide association studies. Lane and colleagues (Lane et al., 2016) report 12 loci significant at the genome-wide level that are associated with chronotype in the UK Biobank sample, including loci with previously described roles in the clock (PER2, an ASPS gene, APH1A, RGS16 and FBXL13). These 12 loci accounted for 4.3% of the variance in the extremities of chronotype, which in the UK BioBank is assessed by a single Likert 5 choice self-assessment of diurnal preference (from the question "Do you consider yourself to be…" and answers ranging from "Definitely a morning person" to "Definitely an evening person"). A further study on the UK BioBank cohort reported 16 significant loci associated with morningness, including ones near PER2 and RGS16 which is involved in phototransduction

(Jones et al., 2016). Hu and colleagues (Hu et al., 2016) report 15 loci associated with morningness (assessed with two question parsed into a binary morning or evening responses in the 23 and Me cohort), including 7 loci near genes with known circadian roles such as those encoding vasoactive intestinal polypeptide (VIP), PER3, FBXL3 and hypocretin receptor 2. Across these three studies, 9 loci were common in at least two studies, indicating that genetic factors are important in shaping chronotype and that GWAS approaches are insightful for this question (Kalmbach et al., 2017). Interestingly, a recent study has shown overlap between genetic predisposition for eveningness and bipolar disorder (Melroy-Greif, Gizer, Wilhelmsen, & Ehlers, 2017). Importantly, another recent study using umbilical fibroblast have shown that factors associated with protein turnover are associated with chronotype, indicating that circadian clock-non-specific factors may be important in influencing clock dynamics and shaping chronotype (Gaspar et al., 2017).

Two of the GWAS analyses of the genetic architecture of chronotype also examined genetic overlap between chronotype and ADHD: Lane et al (2016) reported no significant genetic associations for chronotype with genetic risk for ADHD, and Jones et al (2016) reported a similar null finding. Interestingly both studies do report significant associations for the genetic risk scores for chronotype with those for schizophrenia. There are a number of potential reasons for such observations. Firstly, the variance in chronotype accounted for by the identified loci is modest (~4%, Lane et al, 2016), and chronotype is seemingly at most 50% heritable (von Schantz et al, 2015); as such the later chronotype reported in ADHD may be behaviourally and environmental determined to a greater extent than genetically so. Such an interpretation would situate phase-delays/later chronotype associated with ADHD more as "egg" (i.e. results of other ADHD features) rather than as "chicken" (i.e. causal genetic relationship from circadian to ADHD features). As such, delayed circadian phase as might be indicated by later chronotype may provide a target for behavioural therapies designed to

counteract these phase shifts and ultimately to alleviate ADHD symptoms (see section 3). Clock gene polymorphisms may not confer increased stand-alone genetic risk for ADHD diagnosis, but may confer increased risk for ADHD symptom severity in interaction with environmental factors; a recent report utilising random forest regression reported a significant effect of PER3 in interaction with stress in predicting ADHD severity (van der Meer et al., 2017). Another important caveat is that GWAS studies do not detect rare variants with a minor allele frequency of <5% (Kalmbach et al, 2017). As such, rare variants that have been reported to exert large effects on chronotype would not be captured in such analyses (Jones et al, 1999; Patke et al, 2017). Targeted, hypothesis-driven genetic analysis may reveal roles for such rare variants in ADHD. The final caveat in relation to GWAS studies of chronotype to date is that circadian phenotyping has been based on only one or two questions generating categorical scores based on diurnal preference, there is clear potential for loss of statistical power and granularity in assessing subtleties of circadian phenotype that would not be captured in such approaches (Kalmbach et al, 2017).

There are a number of older studies utilising analysis of single gene polymorphisms in clock genes in ADHD samples. Whilst such studies have many well documented weaknesses, including lack of statistical power, failure to account for epistasis and failure to replicate (Farrell et al., 2015), it is interesting to note that specific polymorphisms in circadian genes may result in very strong phenotypes. For example, an uncommon (allele frequency of ~0.1 to 0.6%) SNP in CRY1 leads to a gain-of-function mutation that results in a larger phase delay of the rest/activity cycle that manifests as delayed sleep phase disorder (Patke et al., 2017). A C/T SNP in the 3'-untranslated region of CLOCK rs1801260 was suggested to be associated with chronotype in a candidate gene study (Katzenberg et al., 1998) (although see (Iwase et al., 2002; Johansson et al., 2003; Pedrazzoli et al., 2007), and was subsequently examined in adult ADHD. Kissling et al (2008) report that the T allele was a risk factor for

ADHD psychopathology in adults (Kissling et al., 2008). Xu and colleagues examined the same SNP in adult ADHD and reported that the allele was overtransmitted in ADHD (Xu et al., 2010). C allele in this SNP in CLOCK was also associated with ADHD symptoms in the general population. This association was not mediated through chronotype (Jeong et al., 2014). Of particular interest for these studies is a report that the rs1801260 SNP in CLOCK is associated with altered CLOCK transcript stability and altered CLOCK protein expression; therefore this is likely to be a functional mutation that alters the dynamics of the clock gene cycle and circadian physiology (Shi et al., 2008).

Another clock gene polymorphism that has received considerable interest is the 4/5 variable number tandem repeat (VNTR) polymorphism in PER3 (Dijk & Archer, 2010). This VNTR has been associated with chronotype, sleep homeostasis and various psychiatric disorders (Archer et al., 2010). The VNTR in PER3 has been associated with difference in executive function (planning performance assayed by the Tower-of-London task; (González-Giraldo et al., 2015)). Further, a SNP in PER3 has recently been linked with ADHD in adults (van der Meer, et al., 2017). As such, PER3 may represent an interesting locus for future study in the genetic overlap between circadian function and ADHD. Other promising associations with clock genes that may be pertinent to ADHD include an association with a SNP in PER2 with reward in healthy adolescents (Forbes et al., 2012) and a SNP in PER1 predicting problematic alcohol use (Baranger et al., 2016). Future work will hopefully address further the genetic overlap between the circadian system and ADHD, in order to better understand the nature of the links between circadian timing and ADHD, and to offer new targets for experimental monitoring and even therapeutic targeting.

The behavioural role of clock genes can be studied using reverse genetic approaches in animal models, in which candidate genes are knocked out or altered (Merrow, Spoelstra, & Roenneberg, 2005). A number of clock gene knockout animals show hyperactivity as part of

their behavioural phenotype, as well as various cognitive alterations. Mice carrying the dominant negative CLOCK mutation show mania-like behaviour, including hyperactivity, decreased sleep, lowered depression-like behaviour, reduced anxiety and an increased reward value in association with elevated dopaminergic activities in the central tegmental area (McClung et al., 2005; Roybal et al., 2007). However, this line of inquiry is complicated by the lack of well validated animal models of ADHD, and the fact that hyperactivity as observed in many models may be a highly non-specific phenotype and not particularly relevant to ADHD-related processes (Carvalho, Vieira Crespo, Ferreira Bastos, Knight, & Vicente, 2016).

A challenge in all studies of circadian function in humans is which, and how many, phase biomarkers can and should be examined (Roenneberg & Merrow, 2016). Given that SCN, and other central tissue, cannot be accessed in such studies as one would in animal studies, investigators seek to assay peripheral oscillators that can be reasonably sampled. One method is to measure circadian differences within and between populations in tissue biopsies yielding primary skin fibroblasts. Individual circadian characteristics are manifested in both central and peripheral oscillators (Brown, et al., 2005), and as such skin fibroblasts may serve as useful substrate for the analysis of molecular circadian function. In fibroblasts transfected with a bmal1::luciferase reporter, period length is influenced by culture conditions (e.g. temperature, concentration of serum in growth medium), but cells displaying short- and long-period lengths retain their relative values under all conditions and period length is also associated with chronotype (Brown, et al., 2005). Alterations in per2::luc rhythms have also been reported in fibroblasts derived from patients with bipolar disorder, and these factors predict responses to lithium (McCarthy et al., 2013). Recently, a study by Hida et al., showed that an in vitro fibroblast rhythm assay accurately describes circadian behaviour of patients with two types of circadian rhythm sleep disorders - delayed sleep-wake phase disorder

(DSWPD) and non-24-hour sleep–wake rhythm disorder (N24SWD) (Hida, et al., 2017). Patients in this study received a four week chronotherapy (bright light therapy + melatonin/melatonin receptor agonist administration). Longer in vitro period predicted poorer response to chronotherapy in patients with N24SWD (Hida, et al., 2017). This and additional studies (Vanselow et al., 2006), suggest that in vitro fibroblasts rhythm assays may provide a valid tool to assess individual genetic characteristics in the biological clock of different populations. Moreover, multiple pre- post- treatment fibroblast samples may contribute to the evaluation of the efficacy of the phase-shifting treatments, including LT and melatonin administration. To our best knowledge, there are no studies reporting usage of fibroblast assays in ADHD diagnosis; given previous indications of clock gene expression changes in ADHD (Baird, et al., 2012) such approaches may yield important insight into the alterations of circadian processes at the molecular level in ADHD.

Cyclic production of pineal melatonin, released by the pineal gland in the absence of blue light via the sympathetic system, informs the clock about photoperiod (e.g., day length)(Stehle, von Gall, & Korf, 2003). As the sympathetic drive to the pineal is gated through the SCN, the time of onset of melatonin biosynthesis under dim light conditions is a very useful phase-marker (Keijzer, Smits, Duffy, & Curfs, 2014). Melatonin may play an important role in the rhythmic clock gene expression (CLOCK, BMAL1, PER1-3, CRY1-2) (Dardente et al., 2003; von Gall et al., 2005), and in various neurological functions and stress response (Hardeland, Madrid, Tan, & Reiter, 2012). Exogenous melatonin and melatoninergic agonists are shown to entrain the sleep-wake cycle, advance endogenous melatonin secretion and enhance total time asleep in children with ADHD and chronic sleep onset insomnia (Chamorro, Lara, Insa, Espadas, & Alda-Diez, 2017; Van der Heijden, Smits, Van Someren, Ridderinkhof, & Gunning, 2007). Further, adults with ADHD with chronic sleep onset insomnia show delayed onset of melatonin secretion (Bijlenga et al., 2013; Van

Veen, et al., 2010), indicating a delayed phase in a SCN-derived signal. Other rhythmic endocrine signals also show alterations in ADHD; cortisol, which shows a strong 24 rhythm driven by the SCN, shows a phase-delay relative to wake-time in adult ADHD (Baird, et al., 2012), and changes in the diurnal cortisol profiles have been linked with alterations in arousal levels in children with ADHD (Imeraj et al., 2012). Therefore, assessment of rhythmic endocrine function in ADHD, and its relationship to ADHD symptom severity and ADHD medication, represents an important substrate for future investigation.

Light treatment for circadian alignment

Light is the primary synchronizer of the circadian timing system (Hughes, et al., 2015). Visible light has a wavelength spectrum of 380 (violet) to 760 (red) nm. The intensity of sunlight, depending on geographical location and season of the year, range between 7,000-100,000 lux (Roenneberg, Kantermann, Juda, Vetter, & Allebrandt, 2013). The effects of timing (Czeisler et al., 1986), duration (Chang et al., 2012), intensity (Boivin, Duffy, Kronauer, & Czeisler, 1996) and wavelength (Revell, Arendt, Terman, & Skene, 2005) of light stimuli on the human sleep-wake cycle are well established in a variety of measures, including phase resetting and the suppression of the sleep promoting hormone, melatonin (Chellappa, Gordijn, & Cajochen, 2011). The light-induced entraining is mediated via intrinsically photosensitive retinal ganglion cells (ipRGCs) that project to the SCN in the hypothalamus. The ipRGCs contain melanopsin, an opsin-like protein, most sensitive to blue light (the shortest wavelength of the visual spectrum) (Hankins, Peirson, & Foster, 2008). However, ipRGC light response is a composite one, influenced by both the extrinsic (rod/cone) and the intrinsic (melanopsin) activation and ipRGC may play a role in visual image formation (Allen, Storchi, Martial, Bedford, & Lucas, 2017). Light, via response of ipRGCs to its spectral properties and intensity, induces a variety of non-visual responses, e.g.,

raising alertness, pupil constriction and suppression of pineal hormone melatonin release (Debra & Josephine, 2006).

Thus, short wavelength blue light (460 nm) possesses greater phase shifting potential than the rest of the visible light spectrum (Lockley et al., 2003, Warman et al., 2003, Wright et al., 2004). Currently, there are no standardized guidelines for the application of light therapy. Based on laboratory and field studies, light therapy should be sufficiently bright (2,000-10,000 lux) to elicit a clinically significant response and should last long enough (>30 min) (van Maanen, Meijer, van der Heijden, & Oort, 2016). Blue light as an environmental factor has been shown to be toxic to rod photoreceptors when the retina is exposed to either high light intensities or to continuous light over a long period of time (Lack, Bramwell, Wright, & Kemp, 2007; Youssef, Sheibani, & Albert, 2011). Therefore, long-term users of bright light therapy lamps should be screened by ophthalmologists, and those with pre-existing retinal conditions or other risk factors should abstain from bright light (BL) therapy (Youssef, et al., 2011).

Natural daylight is considered the strongest zeitgeber for the circadian clock (Wright et al., 2013). Effects of daylight are different from the artificial light and, in particular, BL used in traditional light treatments, in several aspects. (i) In nature, dark-light transitions are always gradual, giving biological systems time to adjust; graduate light exposure has been shown to be an important factor in the photic entrainment of the biological clock (Endo, Kripke, & Ancoli-Israel, 2015; Grandner, Kripke, Elliott, & Cole, 2013). Light-detecting neurons in the circadian system have response characteristics suitable for detection of slow changes in light intensity and spectrum during twilight (Endo, et al., 2015; Grandner, et al., 2013; Usui, 2000). Exposure to BL, even through closed eyelids, was shown to be effective for melatonin suppression (Figueiro, Plitnick, & Rea, 2014; Terman & Terman, 2006). Studies that examined rhythm-entraining properties of artificial twilight and fluctuating light

intensity cycles, underscored the importance of gradual transition between light and darkness for circadian rhythm entrainment in animal models and humans (Avery et al., 2001; Boulos, Macchi, & Terman, 2002; Usui, 2000; Van De Werken et al., 2010). (ii) Colour (spectral) qualities of natural daylight are rich and dynamically changing, while properties of BL used in therapy protocols and in ambient artificial lighting are usually invariable and thus biologically insufficient (Beute & de Kort, 2014; Hye Oh, Ji Yang, & Rag Do, 2014; Terman & Terman, 1999). (iii) Cumulative amount of light during the day impacts human circadian behavior - geographically defined amount of solar irradiation is linked to distributions of chronotypes in population, with living at higher-latitudes areas predisposes to eveningness (Leocadio-Miguel et al., 2017). In line with the latter, lower prevalence of ADHD was recently associated with geographic areas of higher solar intensities (Arns, van der Heijden, Arnold, & Kenemans, 2013). In general, modern people spend increasingly more time indoors, where ambient light is orders of magnitude lower in intensity compared to outdoor light on a clear day (Roenneberg, et al., 2013). Despite the importance of daylight for human wellness and functionality, the neuropsychological consequences of exposure to natural light in comparison to interventions using artificial light are currently poorly understood and the potential of exposure to daylight has not been systematically evaluated both in healthy and clinical populations. Thus, the mainstream of light treatment engages protocols of exposure to artificially generated BL (Terman & Terman, 1999).

The susceptibility of the circadian clock to be shifted by time-specific light exposure is thoroughly studied and is broadly utilized in treatment protocols of sleep-phase and depressive disorders, e.g., SAD (Gooley, 2008; Kaladchibachi & Fernandez, 2018; Oldham & Ciraulo, 2014). Long-term light interventions effectively advance sleep onset time (van Maanen, et al., 2016; Watanabe, Kajimura, Kato, Sekimoto, & Takahashi, 1999) as well as result in less sleepiness after awakening in neurotypical adults with DSPD (Lack, et al., 2007;

Van De Werken, et al., 2010), for a review see (Figueiro, 2016). Wu et al. (2009) treated patients with bipolar disorder with three interventions: sleep deprivation, BL and sleep phase advance. All three non-invasive interventions result in depression decrease (Wu et al., 2009). A study with patients suffering from non-seasonal major depressive disorder observed a positive effect of BL therapy, too. Treatment with BL, either as monotherapy or combined with medication (fluoxetine) showed a consistent effect (Lam, Levitt, Levitan, & et al., 2016). Simulated dawn was proposed as an adjunct and even alternative to BL therapy or medication in the treatment of SAD (Avery, et al., 2001; Terman & Terman, 2006). In addition to easing compliance, naturalistic dawn simulation eliminates possible ocular adverse effects due to exposure to high intensity blue light of conventional BLT protocols (Terman & Terman, 1999).

One inherent problem of bright light studies is the choice of an appropriate placebo condition (Eastman, Young, Fogg, Liu, & Meaden, 1998). Several types of placebo or a combination of them are used in placebo-controlled LT studies: dim red light (as opposed to bright blue light), differently timed light (evening vs. morning), an inert placebo (a light box emitting no visible light) or an inert (deactivated) negative ion generator (for examples see (Chojnacka et al., 2016; Eastman, et al., 1998; Sit et al., 2018)). Indeed, due to the lack of an obvious type of placebo treatment, LT studies have been extensively criticized for their flawed experimental design. And yet, at least for the treatment of seasonal and non-seasonal depression, an accumulated bulk of randomized and double-blind clinical trials approves the utility of LT and invites further studies in other psychiatric, neurodevelopmental and neurocognitive disorders (for review see (Kaladchibachi & Fernandez, 2018)).

Most patients with ADHD demonstrate delays in sleep-wake rhythms and irregularities in melatonin and cortisol production times compared to healthy controls. Considering the fact that ADHD has high co-morbidity with depression (Amons, Kooij,

Haffmans, Hoffman, & Hoencamp, 2006; Turgay & Ansari, 2006), is strongly associated with delayed sleep phase syndrome (Amons, et al., 2006; Baird, et al., 2012; Coogan & McGowan, 2017; Turgay & Ansari, 2006), and given an association between ADHD prevalence and solar intensity at geographic loci (Arns, et al., 2013), the body of literature on the effects of light therapy in ADHD is currently very limited.

A three-week trial of light therapy (LT) to a group of 29 adults with ADHD (Rybak, McNeely, Mackenzie, Jain, & Levitan, 2006) used a full-spectrum fluorescent light box that emitted 10,000 lux, for half an hour each morning, showed that morning BL therapy did help alleviate subjective reports of deficits in maintaining effort and arousal, while improving problems with inattention. Furthermore, neuropsychological testing further confirmed that LT produced significant improvements on attentional functioning which was shown in basic auditory attention span as well as for 2 key components of the Conner's' Continuous Performance Test (CPT-II), indicating improvements in impulsivity and behavioural inhibition. Circadian shift towards morningness was shown in many of the participants (Rybak, et al., 2006).

A two-weeks LT in the morning (30-min morning 10,000 lux exposure 3h after mid-sleep time) in pharmacologically treated participants with ADHD (with different, individually prescribed drugs) significantly advanced the phase of dim light melatonin onset (DLMO) and mid-sleep time (Fargason et al., 2017). These phase advances correlated with decreased total scores in ADHD rating scales as well as hyperactivity-impulsivity indices (Fargason, et al., 2017). Even a single week of LT (1h at 9:00 AM, 2500 lux) in adolescents with ADHD, who were medicated (40 mg Methylphenidate daily) and engaged in psychotherapy, was successful (Niederhofer, 2013). Behavioural improvements were found in both for the Conner's inattention score and in the hyperactivity score. Moreover, evening melatonin levels increased post-treatment (Niederhofer, 2013).

Compared to the long-term effects of light on human circadian rhythms, little attention has been paid to its acute alerting action. High intensity light exposure acutely reduces subjective sleepiness, improves well-being and neurobehavioral performance, reduces attentional lapses, and activates the waking electroencephalogram (EEG) (Badia, Myers, Boecker, Culpepper, & Harsh, 1991; Beute & de Kort, 2014). These alerting effects appear to be dose dependent, such that higher illuminances have greater immediate effects (Cajochen, Zeitzer, Czeisler, & Dijk, 2000). Significant advance of DLMO was shown following a single morning exposure to BL during morning hours (>3000 lux) (Kozaki, Toda, Noguchi, & Yasukouchi, 2011).

Surprisingly, light as acute alerting agent was not clinically studied in ADHD. We hypothesize that exposure to BL in ADHD may produce effects similar to other types of sensory stimulation during wakefulness. Various types of extra-task sensory stimulations were reported beneficial for cognitive performance of children with ADHD, e.g., background linguistic noise during a reading/arithmetic task (Zentall & Shaw, 1980), pictures during a continuous performance auditory task (Zentall & Meyer, 1987), background music during arithmetic tasks (Abikoff, Courtney, Szeibel, & Koplewicz, 1996) and auditory white noise during a visually cued Go/NoGo task (Baijot, et al., 2016). If sensory stimulation in one or more forms may enhance cognitive functioning of people with ADHD, similar acute effects may be found for light treatment, especially given that light positively affects attention and performance in neurotypical adults (Beute & de Kort, 2014).

It has been previously suggested that core cognitive processes, such as memory consolidation, are extant but under-engaged in adults with ADHD and that this potential can be unveiled in specific bio-behavioural conditions, contingent on the individual's chronotype (Korman, et al., 2017), - e.g., by scheduling of training session to evening. A different, chronotherapy approach by appropriately timed LT, may eliminate the need to adapt

conditions of training and performance to chronotype by long-term phase advancement of the clock. LT is associated with dopaminergic (Kim et al., 2017), adrenergic (Bowrey, James, & Aston-Jones, 2017) and serotonergic (Li, 2018) brain circuits activation, pathways directly associated with learning, executive functioning and mood. The SCN's endogenous ~24h time-generator comprises a dynamic series of functional brain states, which gate neuronal plasticity following daily experiences. The circadian clock, the reward system, and memory processes have many in common: light acts on all three systems through MAPK signalling pathway (Iyer, Wang, & Gillette, 2014) and all three are affected by the HPA-axes via cortisol, thereby leading to short-term changes (Albrecht, 2011; Eckel-Mahan et al., 2008). Moreover, most clock genes are expressed in brain areas that are associated with learning, memory, and reward (Albrecht, 2011), such as the amygdala (Lamont, Robinson, Stewart, & Amir, 2005), the hippocampus (Jilg et al., 2010; Wakamatsu et al., 2001) and the ventral tegmental area (Hampp et al., 2008).

Conclusions

ADHD is a common neuropsychiatric disorder affecting both wake and sleep phases of the diurnal cycle. Altered function of clock genes in ADHD is so far poorly understood, but mounting evidence suggests that atypical brain maturation and neurogenesis processes, sleep problems and the emergence of cognitive, executive functioning and self-regulation symptoms present in ADHD are at least partially subserved by circadian disruption (Charrier, Olliac, Roubertoux, & Tordjman, 2017; Kobayashi, Ye, & Hensch, 2015). Thus, on the one hand, studies showed that genetic risk factors exist, e.g., associations between ADHD and other neuro-developmental and psychiatric disorders and polymorphism (rs1801260) at the 3′-untranslated region of the CLOCK gene, predispose to eveningness and sleep problems. On the other hand, the susceptibility of the circadian system to phase shift by timed BL exposure has broad cost-effective potential implications for the treatment of core symptoms

of ADHD as well as for augmentation for prevention of psychiatric comorbidities in ADHD. Moreover, for the non-responders to pharmacological treatment, introduction of LT protocols may be of outmost importance. Further studies are needed to evaluate therapeutic outcomes of different types of light therapy (blue-light emitting boxes vs. simulated dawn vs. natural daylight) and to explore causality between BL therapy and changes in circadian gene expression. A suitable model for studying circadian gene expression and molecular circadian function could be human skin fibroblasts. A recent study using BL therapy showed a poorer response to chronotherapy predicted by longer in vitro period in patients with N24SWD (Hida et al., 2017), suggesting that the period length is associated with chronotype and the fibroblasts rhythm correlates with circadian behaviour. Combined approach of assessment and phase shifting the circadian rhythm introduce new revenues for the integrated diagnosis, treatment and the evaluation of treatment of ADHD.

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