Pop-Jordanova, N. Zorcec, T., Demerdzieva, A., Gucev, Z., 2010. QEEG Characteristics and Spectrum Weighted Frequency for Children Diagnosed as Autistic Spectrum Disorder. Nonlinear Biomedical Physics 4:4.

Sela, R., Shaked-Toledano, M., 2014. Neurofeedback Treatments Enable the EEG-Normalization and Total Seizure Control of Epilepsy - A Case Study. NeuroConnections, Spring, p. 56.

Sterman, B., Egner T. 2006. Neurofeedback Treatment of Epilepsy: from Basic Rationale to Practical Application. Expert Review of Neurotherapeutics 6(2), p. 247.

Tan, G., Thornby, J., Hammond, C., Strehl, U., Canady, B., Arnemann, K., Kaiser, A. 2009. Meta-Analysis of EEG Biofeedback in Treating Epilepsy. Clinical EEG and Neuroscience 40(3), p. 173.

Thornton, K. 2000. Improvement/Rehabilitation of Memory Functioning with Neurotherapy/QEEG Biofeedback. Journal of Head Trauma Rehabilitation, 15, p. 1285.

WHAT'S SLEEP GOT TO DO WITH IT? CIRCADIAN RHYTHM SLEEP DISORDER, ADHD AND NEUROFEEDBACK.

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Abstract

Recent evidence points to the increasingly important role of sleep disturbance in ADHD. Circadian phase delay, resulting in delayed sleep onset, has been consistently described with causality implied for a large subgroup with Attention Deficit Hyperactivity Disorder (ADHD). The likelihood of varied and numerous causations in ADHD, the high prevalence of sleep disorders and the likely etiological/pathogenetic role of sleep disorders for a large subgroup with ADHD encourages a personalized medicine approach, particularly by assessing sleep and identifying biomarkers to assist in identifying subgroups which can enable a more personalized treatment. Psychostimulants are the mainstay of pharmacological treatment of ADHD, but do not assist sleep problems and can in fact exacerbate them. In a large subgroup with ADHD, psycho-education and sleep hygiene, CBTi and chronotherapy also have an important role to play in treating ADHD symptoms associated with sleep disturbance. Neurofeedback (operant conditioning of EEG), may have specific and lasting effects on sleep, and in turn ADHD symptoms, with the effect shown to be mediated via the normalization of sleep. This review article summaries and reports on some of the accumulating evidence for the role of sleep in ADHD and outlines various methods for assessment and intervention.

Keywords: sleep; delayed phase sleep disorder; circadian rhythm; dopamine; vigilance arousal; hypocretins; ADHD; neurofeedback

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1. Introduction

Psychostimulant medication remains the mainstay of treatment for Attention Deficit Hyperactivity Disorder (ADHD). Nevertheless, the positive effects on ADHD symptoms often diminish over time (Molina et al., 2009), side effects are common (Wang et al., 2013) and the medications can reduce sleep duration and increase sleep onset latency in some. Concurrent sleep problems have been shown to attenuate the response to stimulants, while conversely longer sleep duration is associated with a better response to ADHD medication (Santisteban et al., 2014; Morash-Conway et al., 2017). Longer duration of sleep is also associated with better response to antidepressant medications in people suffering from major depressive disorder (Arnedt et al., 2016), suggesting to a role for sleep in treatment efficacy.

There is a similarity in the symptoms of sleep disorders and those observed during jet lag, shift-work etc, and the symptoms of ADHD – that is, an inability to maintain focus and attention; impaired learning; behavioral difficulties manifesting as impulsivity and reactivity with a bias towards habitual or auto-regulatory behaviors and mental health symptoms such as anxiety and depression (Wolfson A, Carskadon M, 1998) and self harm (Lui X, 2004)). Children with ADHD are reported to have altered sleep architecture, spending comparatively more time in stage 1 sleep (Diaz-Roman et al., 2016) and also a reduced amount of sleep spindles have been reported (Saletin et al., 2017). More daytime sleepiness is also reported in this group (Langberg et al., 2017). The severity of sleep problems has been shown to correlate with cognitive dysfunction (Sciberras et al., 2015), while delayed sleep onset and poor sleep efficiency has been associated with impulsivity in particular (McGowan and Coogan., 2018). Persistence of childhood ADHD into adolescence and adulthood is predicted by the persistence and severity of sleep problems (Gregory et al., 2017; Cadman et al., 2016). In a recent study, shorter sleep duration correlated with more internalizing and externalizing behavior problems in children and adolescents, with shortened sleep duration being causal of such ADHD symptomatology as inattention, daytime sleepiness and oppositionality (Becker et al., 2018). Conversely, longer sleep duration is correlatively associated with better school performances and cognitive functioning (Astil et al., 2012). Sleep restriction is associated with poorer academic performance (Zerbini and Merrow., 2017) and interventions that have enabled increased sleep duration (e.g. delayed school start times) have reported improvements in mood and academic performance (Boergers et al., 2014; Owens et al., 2010) . Restricted sleep duration is causally linked to inattention in both those with ADHD (Becker et al., 2018; Arns and Vollebregt, in press) and without ADHD (Axelsson et al., 2008; Belenky et al., 2003: van Dongen et al., 2004). Sleep restriction is also linked to mood dysregulation, self-harm and impulsivity (Bernert and Joiner. 2007; O'Brien, 2009.; McGowan and Coogan., 2018) suggesting an important role of sleep interventions in the treatment and prevention of self-harm behaviours and mood disorders. Walker (2017, pages 147-148) suggests that the sleep restriction is associated with both hyper-activation of the dopaminergic striatum and hypo-activation of the prefrontal areas (resulting in emotional and hedonic instability) which may be an aspect of the underlying neurophysiological process manifesting in emotion dysregulation and impulsive behaviour. Disordered breathing in sleep, snoring (e.g., due to enlarged adenoids) and obstructive sleep apnoea (OSA) are associated with both inattention (Sedky et al., 2014) and hyperactivity (Silvestri et al., 2009) with the same relationship also shown in a general population sample (Bonuck et al., 2012). Treatment with tonsillectomy/cpap results in improvement of the ADHD symptoms (Sedky et al., 2014; Johnstone et al., 2001).

2. ADHD and sleep

A clear relationship between ADHD and sleep disturbances has been reported (Diaz-Roman et al., 2008) and on the group level, an association between ADHD and the delayed onset of sleep has been described (Coogan and McGowan, 2017) with delayed onset of sleep being shown as an important factor for at least some

with ADHD (Arns and Kenemans, 2012). Sleep onset insomnia has even been noted in the majority of ADHD patients before the age of three (Van der Heijden et al., 2005) with the strong suggestion that it is the persistence of this sleep disruption over time that eventually manifests in the clinical syndrome of ADHD. Disruption of brain network organisation and functioning involved in sleep and cognitive functioning, may lead to persistence of the symptoms and behaviours identified with ADHD into adolescence and adulthood (Kurth et al., 2016). A psycho-educational intervention to address sleep onset insomnia reported a decrease in ADHD symptoms (Corkum et al., 2016).

One of the causes of a delay in sleep onset is thought to be the absence of strong zeitgebers. Variation in natural daylight is the strongest zeitgeber of the circadian rhythm [for review, see (Roenneberg & Merrow, 2016). Note that the prevalence of ADHD has been shown to vary with daytime natural light exposure, i.e. with solar intensity (Arns et al., 2013). Lighting factors such as domestic lighting sources (LED, halogen and fluorescent lights) and the use of blue light emitting devices shortly before bedtime are associated with suppression and delay of production/release of melatonin (Wood et al., 2012; Cajochen et al., 2011) resulting in delayed sleep onset (Custers et al., 2012; Walch et al., 2016), and night-time blue light exposure has an effect even if eyes are closed (Figueiro et al., 2014). Fixed school/work starting times invariably means that delayed onset of sleep results in shorter duration of sleep (van don Bulch et al., 2004; Walch et al., 2016).

Children's sleep duration has declined by an average of 75 minutes over the past 100 years (Matricciani et al., 2012) and sleep restriction is associated with reduced school performance, impaired executive functioning and behavioural impulsivity (van Dongen et al., 2003). A recent study (Becker et al, 2018) was able to conclude that shortened sleep duration had a causal role in sleepiness, inattention and other features of ADHD symptomatology. Chronic sleep disruption of less than six hours a night is associated with cumulative, significant cognitive and behavioural deficits, of which the person is unaware (van Dongen et al., 2003).

A recent study demonstrated a pathway where evening blue light exposure delays sleep, thereby reducing sleep duration, which, in turn, results in increased teacher-rated symptoms of inattention (figure 1) (Vollebregt et al., Under Review).

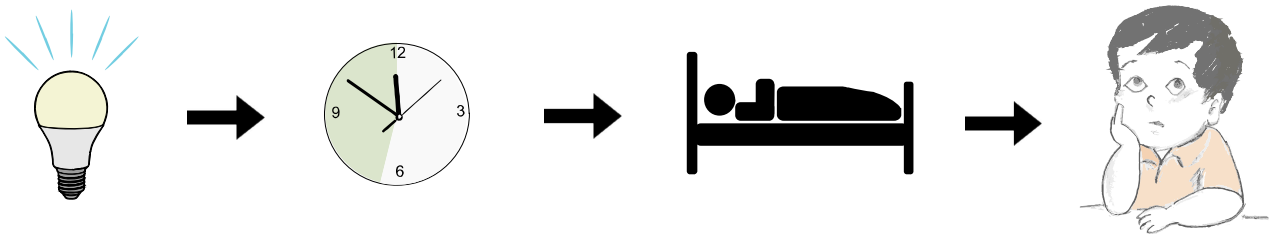

Figure 1. A pathway is depicted where LED light exposure is positively associated with amount of sleep onset delay, which in turn is negatively related to sleep duration, which ultimately leads to worsening of attention.

There are high rates of a range of sleep disorders in the child and adult ADHD patient populations; a 20% prevalence of OSA (Silvestri et al., 2009); a 20% prevalence of restless legs (Konofal et al., 2010; Silvestri et al., 2009) and a 73-78% prevalence of delayed onset circadian rhythm sleep (van der Heijden et al., 2005, 2007; van Veen et al., 2010; Arns et al., 2014). Both snoring (e.g., due to enlarged adenoids) and OSA are associated with core features of ADHD - inattention (Sedky et al., 2014) and hyperactivity (Silvestri et al., 2009; for subclinical disordered breathing sleep, Vollebregt et al., under review)), and specific treatment has been

shown to result in the improvement of ADHD symptoms (Sedky et al., 2014; Johnstone et al., 2001; Huang et al., 2007).

In line with children's declining sleep duration, indicators of drowsiness have increased over recent years; excess theta (4-8Hz) activity or an increased theta to beta ratio (TBR), often described as EEG slowing, have been reported (Arns et al., 2012). An increased absolute power in the theta band is a consistent reported EEG finding in ADHD (eg, Bresnahan et al., 1999; Clarke et al., 1998) and this slower EEG rhythm can be regarded as indicating impaired vigilance regulation and hypo-arousal (Sander et al., 2010). Other EEG phenotypes, such as frontal alpha, also reflecting impaired vigilance, have also been reported in ADHD (Arns, 2012). Sleep onset insomnia and inattention are linked to the excess theta and frontal alpha and spindling excessive beta (SEB) is linked to sleep maintenance problems and impulsivity (Arns et al., 2015). The EEG vigilance model is based on the progressive slowing of the EEG as one drifts towards sleep, with several phenotypes being described (Hegerl and Hensch, 2014) which can be related to a range of clinical conditions. It is this labile or unstable pattern that is often apparent in ADHD (Sander et al 2010), indicating significant drowsiness, and is thought to be the outcome of persistent sleep restriction over time (Beebe et al., 2010).

3. The Visual System and The Circadian System

The circadian rhythm orchestrates the temporal pattern of all biological processes – neuropsychological, behavioral, gene expression, metabolic, hormonal, immunological etc. Genetic variations in clock genes are reflected in individual chronotypes. It is important to consider whole of body entrainment of the circadian rhythm. Entrainment is the process of synchronisation between external/environmental time of day as signalled by zeitgebers, especially light-dark, and internal time. Optimal entrainment is when external time and internal time are approximately equal. Internal timing is orchestrated by the SCN entraining the peripheral cellular and organ clocks, developing a phase relationship between the central and peripheral clocks. Entrainment is readily disrupted by the weak zeitgebers of our urban lifestyle and further disrupted by the social/work demands and other non-sleep promoting behaviours etc, and the related required use of alarm clocks so that internal misalignments and sleep deprivation are common, resulting in social jetlag. Problems with circadian entrainment at any/all levels of the whole body resulting in suboptimal phase misalignment is considered to be related to most of our current health problems (Zee P, 2015)

As indicated above, variation in natural daylight is the strongest of a range of zeitgebers of the circadian rhythm [for review, see (Roenneberg & Merrow, 2016)]. Besides the well-known rods and cones photoreceptor cells in the retina that are responsible for night and color vision, there are also retinal photoreceptor cells that are responsible for the non-image forming perception of light intensity. These cells modulate, among others, the pupillary reflex, the release of melatonin and dopamine, and project via the retinohypothalamic tract to the suprachiasmatic nuclei (SCN) (Schmidt and Kofuji 2009). With this, the retina has a key role in circadian rhythmicity with both melatonin and dopamine being produced in small amounts in the retina (relative to pineal melatonin production), at night and in the day respectively. The retinal and brain regulation of dopamine and melatonin are related. Melatonin and dopamine function as neuromodulators of retinal physiology (e.g. dopamine adjusting for daytime vison, melatonin for night-time vision), with melatonin having the dominant role (Tosini et al., 2012). Retinal melatonin must be suppressed during the day to prevent melatonin intensified photoreceptor oxidation and damage to the retinal cells thought to contribute to macular degeneration, with melatonin also playing a role in the regulation of intraocular pressure. At night melatonin also influences retinal cell replacement and renewal (Tosini et al., 2012).

It is well known that retinal ganglion cells are involved in the pupillary response, respond to blue light intensity and project to the suprachiasmatic nucleus (SCN), resulting in melatonin release from the pineal gland, and the sleep promoting GABAergic neurones in the ventrolateral preoptic nucleus and superior colliculus (part

of the dialectic regulation of the vigilance arousal system), thereby playing a key role in circadian rhythm entrainment of the many physiological body clocks.

The retinal ganglion cells are interconnected with the retinal dopaminergic amacrine cells (Mendoza and Challet, 2014; Stone et al., 2013). Retinal dopamine is thought to play a role in ocular development which in turn may be related to the visual problems reported in ADHD (see below). The DRD4 7R allele is considered to be a genetic risk marker of ADHD (Nikolaidis and Gray, 2010) and is related to a significantly lower affinity for dopamine at the post-synaptic membrane (Ding et al., 2002) and a reduced capacity in the cellular processing in response to illumination (Ashargi et al, 1995). Carriers of this allele are also reported to have greater daytime sleepiness (Jawinski et al, 2016). The expression of DRD4 receptors, which occur in both the retina and pineal gland, varies with the circadian cycle (Kim et al., 2010).

At both the retinal and central levels, melatonin and dopamine are under circadian influence (Parekh et al., 2015) with opposing roles in the regulation of the circadian rhythm (Mendoza and Challet, 2014; Mundey et al., 2005; Iuvone et al., 1978). Dopamine which is predominately synthesised and released in the morning (Iuvone et al., 2005; Doran et al., 1990) inhibits melatonin release and vice versa (Green and Besharse, 2004). Impaired retinal dopamine synthesis is associated with circadian rhythm fluctuations (Wirz-Justice, 1984) suggesting an important role of dopamine in sleep-wake regulation.

Retinal dopamine is produced in the retinal amacrine cells and its synthesis and release are triggered by blue light activation of D2 receptors which also signals CLOCK and BMAL 1 activation (Yujnovsky et al., 2006). Melatonin, however, controls the amacrine sensitivity to blue light. In nocturnal mice for instance, light exposure inhibits behaviour and promotes sleep (Hubbard et al., 2013). Sleep deprivation is linked to HPA-axis activation and reduced sleep duration and slow wave sleep, and increased awakenings. The morning peak of the diurnal variation of cortisol is driven by the suprachiasmatic nucleus (SCN) via corticotropin releasing factor (CRF) signalling which also activates the locus coeruleus (LC) and striatum resulting in increased noradrenaline and dopamine release. This reflects the diurnal control of the Hypothalamic Pituitary Adrenal Axis (HPA axis) which is also has a role in the regulation of sleep and wakefulness. Corticotropin releasing factor (CRF) and cortisol are normally suppressed by melatonin as part of the process of enabling sleep to emerge and melatonin is also involved in the emergence of slow wave sleep and the related growth hormone surge (Buckley and Schatzberg, 2005). The hypocretin neuronal system which receives input from other hypothalamic areas, the environment, the homeostatic state and the limbic system has a key modulating and orchestrating role of these many signals for arousal and sleep, and widespread projections throughout the brain, to enable situation/task appropriate vigilance/arousal – apparent in REM and NREM sleep and sleep to wake transitions as well as appropriate arousal in the awake condition, and thus also providing a systems account of the daytime hypo-arousal and the night time hyperarousal and disordered sleep that are considered core aspects of ADHD (de Lecea L and Huerta R, 2014; Eban-Rothschild A et al, 2017; de Lecea Let al, 2012; de Lecea L, 2012).

There is a complex relationship between the dopaminergic amacrine cells, the retinal ganglion cells, the SCN and the LC, striatum, melatonin and sleep spindles. The LC plays a role in vigilance regulation and there are connections between the SCN and the LC, with the latter also having a role in the generation of sleep spindles (Sinha, 2011). Noradrenaline binding to receptors on the pineal gland promotes the synthesis and release of melatonin by the pineal gland. D4 receptors are expressed in the pineal only when there are increased levels of noradrenaline and, in relation to light exposure and dopamine binding to these receptors, modifies noradrenergic signalling, inhibiting synthesis and release of melatonin, contributing to waking up (Gonzalez et al., 2012).

Genetic influences are also relevant. In addition to the above mentioned DRD4 7R genotype, other genes have been linked to both ADHD and the circadian rhythm. The CLOCK gene is linked to lengthening of the sleep/wake cycle as well as ADHD, bipolar and depressive disorders (Xu et al., 2010; Benedetti et al., 2003); the BMAL1 and PER2 genes are also linked to delayed sleep onset and ADHD, and a decrease in circadian

rhythmicity in those with ADHD compared to healthy individuals (Baird et al., 2012). CLOCK and BMAL1 genes are also diurnally expressed in dopaminergic areas of the brain (ventral tegmental area and substantia nigra) with the SCN clock, via various connections, having the entraining role in modulating diurnal variation in dopamine levels (Mendoza and Challet, 2014). Prenatal and postnatal influences (e.g., long term maternal psychostimulant use) disrupts the developmental alteration in the SCN's progressive reduction of responsivity to dopamine and increased responsivity to blue light and melatonin, disrupting the capacity to adequately set the diurnal rhythm.

CLOCK genes have a role in the modulation of response to dopamine (Roybal et al., 2007). Any change in dopaminergic processes, including those related to psychostimulant use, have the potential to alter aspects of this complex system, including SCN functioning, and CLOCK gene expression both in the SCN and the striatum. Methamphetamine strongly activates dopaminergic and noradrenergic systems in the brain (Chio V, Schenk J, 2012), although there may be a dose dependent variable impact on the circadian rhythm (Honma K, Honma S, 2009). Psychostimulants also alter the expression of CLOCK genes in the ventral striatum and the SCN, potentially contributing to a disruption of circadian control by the SCN (Antle et al., 2012; Baird et al., 2013). Of note is that the striatum is heavily populated with melatonin receptors (Uz et al., 2005). In Parkinson's Disease, a dopamine related degenerative neuropathology, circadian rhythm disruptions with increased SOL, excessive daytime sleepiness and restless legs are prominent (Videnovic and Golombek, 2013; Palma et al., 2013), further supporting the idea that rhythmic diurnal dopamine-melatonin synchronization is important in the 'proper' regulation of the circadian sleep-wake cycle.

Other ocular issues reported in ADHD include glare sensitivity (Kooij and Bijlenga, 2014) with more frequent and longer use of sunglasses; refractive errors such as myopia, astigmatism and impaired depth perception (Gronlund et al., 2007; Granet et al., 2005; Mezer et al., 2012; Kim et al., 2014; Banaschewski et al., 2006). Both dopamine and melatonin have a role in optimising diurnal variations in visual acuity (Tosini et al., 2012) and retinal dopamine deficiency is associated with impaired visual acuity (Jackson et al., 2012). Of particular note, visual acuity has been reported to be improved on stimulant medication (Martin et al., 2008). Disruption in the complex circadian control of retinal melatonin and dopamine has also been implicated in a range of ocular abnormalities such as increased intraocular pressure, susceptibility to photoreceptor degeneration from light damage as in macular degeneration as well as the degree of refractive errors in myopia (Ruan et al., 2006).

Circadian dysregulation of dopamine is linked to a range of impulsive behaviors and actions and vulnerabilities as diverse as sexual activity, substance abuse (Parekh et al., 2015) and drug overdose (Baltazar et al., 2014; Raymond et al., 1992). So, there are a range of peptides, melatonin, corticotrophin releasing factor, noradrenaline and dopamine that have a complex relationship and widespread effects that need to be adequately synchronized for optimal functioning. There is a close relationship between circadian rhythm disruptions and substance abuse and dependence. Alcohol dependence disrupts circadian gene expression (Huang et al., 2010) and circadian genes regulate behavioral responses to drugs of abuse, which directly act on the dopaminergic reward systems also regulated by the circadian system. This suggests an additional mechanism of alcohol's sleep disrupting effects, such as its effects on REM sleep via its metabolite aldehyde.

The reports of melanopsin retinal ganglion and retinal amacrine dysfunction highlights the complexity of the interacting, recursive processes involved and encourages a more complex, whole body account of circadian entrainment and the pathophysiological processes accounting for the circadian sleep dysregulation, dopamine dysregulation and ADHD symptoms, particularly within the largest subgroup of ADHD.

4. Personalised Assessments and Individualised Treatments

Symptoms and diagnostic labels are imprecise indicators of causal processes and the corresponding treatments. Hence treatment guidelines based on diagnosis and symptoms lack precision, resulting in a 'stab in the dark/trial and error' approach to treatment. Typically, such an approach also features a profusion of comorbidities, each requiring different treatments and not necessarily beneficial when combined.

Considering the likelihood that ADHD is the result of heterogeneous pathophysiology and is thus likely to comprise several subtypes, this encourages a personalized assessment approach in order to define the most appropriate treatment.

Given that a large proportion of ADHD involves a sleep disorder, sleep assessments are essential. Sleep can be assessed clinically, using a range of questionnaires, actigraphy assessment and EEG/quantitative EEG (QEEG). Where indicated, an overnight sleep study can also be performed. These methods enable identification of possible sleep problems that might be playing a role in the aetiology/pathophysiology of ADHD and its specific impact on each individual. The markers identified in these assessments can enable greater precision in treatment planning with the likelihood of achieving a better outcome. This process of identifying neuromarkers and biomarkers is a feature of the 'personalized' or 'precision medicine' approach (Olbrich et al., 2015). Such assessments are then used to guide a range of chrono-medical interventions including neurofeedback, psychoeducation about sleep hygiene, CBT for insomnia, advice about caffeine and chronotherapy, cpap and other methods to address obstructive sleep apnoea, melatonin supplementation, medication for restless legs to name just a few.

5. Neurofeedback and sleep

Psycho-education, sleep hygiene, CBTi and chronotherapy play an important role in ADHD treatment. However, melatonin (which also increases sleep spindle density during sleep (Dijk et al 1995) and reduces sleep onset latency (Van der Heijden et al 2007)), and chronotherapy have only medium effect sizes and need to be continued in order to achieve any benefit (Rybak et al., 2006; Hoebert et al., 2009). The largest subgroup of sleep disorders in ADHD features a delayed sleep onset and other markers of failure to adequately establish circadian rhythm sleep. Neurofeedback, the operant training of EEG activity, has been shown to have a specific effect on sleep and ADHD symptoms (Arns et al., 2014). Arns et al (2009) have reported that at the group level, both Frequency Band and Slow Cortical Potential (SCP) neurofeedback for ADHD achieve a large effect size for inattention and impulsivity and medium effect sizes for hyperactivity. A more recent meta-analysis (van Doren et al., 2018) indicates that the effects of standard neurofeedback protocols (SMR, Theta-beta and SCP) are maintained at 3-12 month follow up, suggesting persistent effects of this intervention. This latter study noted further improvement in the follow up period after neurofeedback treatment was finished, supporting the notion that cognitive impairments continue to improve following a sustained period of adequate sleep. The effects of SMR neurofeedback in ADHD have been demonstrated to be mediated by the normalisation of sleep prior to the improvement of ADHD symptoms (Arns et al., 2014). A QEEG informed approach would use neurofeedback to target, as indicated, theta, alpha and/or SEB (Arns et al., 2012).

Effective neurofeedback requires strict adherence to the principles of learning and conditioning – so variables such as latency and specificity of reinforcement, shaping and generalisation are essential for learning to take place. In training sleep spindles in sensory motor rhythm (SMR) neurofeedback, training both amplitude and duration is necessary. SMR neurofeedback increases sleep spindle density during sleep, is associated with reduced sleep onset latency (Hoedlmoser et al., 2008), and increased total sleep time (Cortoos et al., 2010), similar to the effects of melatonin. It is considered that both SCP and SMR neurofeedback train the sleep spindle networks (Arns and Kenemans, 2012), although this finding needs to be replicated in well designed and well

powered clinical trials. The density of sleep spindles shows a circadian rhythmicity similar to that of melatonin (De Gennaro and Ferrare, 2003; Dijk et al., 1997).

6. Conclusion

The converging evidence on ADHD suggests there is most often a delayed phase circadian sleep disorder and, at least for some in this group, there may be a combination of genetic variants determining dysfunction in melanopsin photosensitive retinal ganglion cellular functioning and also genetically-related dysfunction in the amacrine and dopaminergic system. These systems alter the dynamics of the interaction with the light-dark cycle and the adequate entrainment of sleep-wake and arousal regulation physiological processes. The role of neurofeedback is clearly becoming more important for this subgroup with ADHD as understanding and specification of this method and supporting evidence of its efficacy continue to emerge.

Given that there is not just one, but several ADHD related sleep disorders playing a pathophysiological role in ADHD symptomatology, there is a need for comprehensive and personalized assessment of sleep in all patients with ADHD. Such a personalized assessment approach allows for a better characterization of the ADHD subgroup, enabling a more individualized treatment with the expectation of achieving better outcome from a more specific treatment.

An appreciation of the complexity of the neurobiology of sleep, wakefulness and arousal also encourages attention to the role of lifestyle/sleep behaviors and habit factors and the likelihood of dysfunction/dysregulation of a wide range of arousal regulation-related systems, such as the hypocretin system, the retinal ganglion- and amacrine dopaminergic cells, resulting in a systemic disruption of sleep-wake and arousal regulation. This should also encourage a fresh and nuanced look at the model of understanding ADHD, at current methods of treatment and a revision of the dominant approach of psychostimulant medication being the only treatment.

A future article will provide an overview of the model of vigilance/arousal regulation involving hypocretins and the relevance of dysfunction in this complex system manifesting in a range of psychiatric disorders including ADHD. Placing sleep and wakefulness and arousal into the complex system of vigilance regulation will potentially provide more of the jigsaw pieces that enable a more adequate apprehension and comprehension of the many variables and their relationships involved in consolidation of sleep and enabling appropriate wakefulness and arousal and foster further personalization of understanding and intervening in ADHD and psychiatric disorders as a systems/network dysregulation problem, rather than consideration of just one neurotransmitter system.

References

Antle M, van Diepen H, Deoer P, Pedram R, Pereira R and Meijer J. 2012. Mehtylphenidate modifies he motion of the circadian clock. Neuropsychopharmacology 37(11): 2446-2445

Arnedt T, Swanson L, Dopp R, Bertram H, Mooney A, Huntley E, Hoffmann R, and Armitage R. J. Effects of Restricted Time in Bed on Antidepressant Treatment Response: A Randomized Controlled Trial. Clin Psychiatry 2016;77(10):e1218–e1225 10.4088/JCP.15m09879

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG theta/beta ratio research in ADHD: A meta-analysis. Journal of Attention Disorders, 17(5), 374-83. doi:10.1177/1087054712460087

Arns M, Connors K, Kraemer H. A Decade of Theta/Beta Ratio Research: A Meta-Analysis. Journal of Attention Disorders. 2012. doi.org/10.1177/108705712460087

Arns, M., de Ridder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis. Clinical EEG and Neuroscience, 40(3), 180–189.

Arns, M., Feddema, I., & Kenemans, J. L. (2014). Differential effects of theta/beta and SMR neurofeedback in ADHD on sleep onset latency. Frontiers in Human Neuroscience, 8, 1019. doi:10.3389/fnhum.2014.01019

Arns M, Swatzyna R, Gunkelman J and Olbrich S. Sleep maintenance, spindling excessive beta and impulse control: an RDoC arousal and regulatory systems approach? Neuropsychiatric Electrophysiology (2015) 2:1

Arns M. 2012. EEG-based personalized medicine in ADJD: Individual alpha peak frequency as an endophenotype associated with nonresponse. Journal of Neurotherapy. 16, 123-14

Arns M & Kenemans J. 2012. Neurofeedback in ADHD and insomnia: Vigilance stabilisation through sleep spindles and circadian networks. Neuroscience and Biobehavoural Reviews, 44, 183-194. doi:10.1016/j.neubiorev.2012.10.006

Arns, M. & Vollebregt, M.A.. Time to wake up: Appreciating the role of sleep in ADHD. Journal of the American Academy of Child & Adolescent Psychiatry 2018, Oct. In press.

Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem. 1995;65:1157-65.

Astil R, Van der Heijden K, Van Ijzendoorn M, Van Someren E. Sleep, Cognition and Behavioural Problems in School Age Children: A Century of Research Meta-Analyzed. Psyhol Bull. 2012

Axelsson, J., Kecklund, G., Åkerstedt, T., Donofrio, P., Lekander, M., & Ingre, M. (2008). Sleepiness and performance in response to repeated sleep restriction and subsequent recovery during semi-laboratory conditions. Chronobiology International, 25(2-3), 297-308. doi:10.1080/07420520802107031

Baird AL, Coogan AN, Siddiqui A, Donev RM, Thome J. Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. Mol Psychiatry. 2012;17:988-95.

Baltazar RM, Coolen LM, Webb IC: Medial prefrontal cortex inactivation attenuates the diurnal rhythm in amphetamine reward. Neuroscience. 2014; 258: 204–10

Banaschewski T, Ruppert S, Tannock R, Albrecht B, Becker A, Uebel H, et al. Colour perception in ADHD. J Child Psychol Psychiatry. 2006;47:568-72.

Becker S, Epstein J, Tamm L, Tilford A, Tischner C, Isaacson, Simon J, Beebe D. Shortened Sleep Duration Causes Sleepiness, Inattention, and Oppositionality in Adolescents with ADHD: Findings from a Crossover Sleep Restriction/Extension Study. Journal of the American Academy of Child & Adolescent Psychiatry. (2018), do: https://doi.org/10.1016/

Becker, S.P., Epstein, J.N., Tamm, L., Tilford, A.A., Tischner, C.M., Isaacson, P.A., Simon, J.O., Beebe, D.W.. Shortened sleep duration causes sleepiness, inattention, and oppositionality in adolescents with ADHD: Findings from a crossover sleep restriction/extension study. Journal of the American Academy of Child & Adolescent Psychiatry 2018, Sep. In press. doi: 10.1016/j.jaac.2018.09.439.

Beebe D, Rose D, Amin R. Attention, learning and arousal of experimentally sleep restricted adolescents in a simulated classroom. Journal of Adolescent Health. 47 (2010), 523-525

Belenky, G., Wesensten, N. J., Thorne, D. R., Thomas, M. L., Sing, H. C., Redmond, D. P., . . . Balkin, T. J. (2003). Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: A sleep dose-response study. Journal of Sleep Research, 12(1), 1-12.

Benedetti F, Serretti A, Colombo C, Barbini B, Lorenzi C, Campori E, et al. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. Am J Med Genet B Neuropsychiatr Genet. 2003;123B:23-6.

Bernert R and Joiner T. Sleep disturbances and suicide risk: A review of the literature. Neuropsychiatr Dis Treat. 2007 Dec; 3(6): 735–743.

Boergers J, Gable CJ, Owens JA. Later school start time is associated with improved sleep and daytime functioning in adolescents. J Dev Behav Pediatr. 2014;35:11-7.

Bonuck, K., Freeman, K., Chervin, R. D., & Xu, L. (2012). Sleep-disordered breathing in a population-based cohort: Behavioral outcomes at 4 and 7 years. Pediatrics, 129(4), e857-65. doi:10.1542/peds.2011-1402

Bresnahan SM, Anderson JW, Barry RJ (1999) Age-related changes in quantitative EEG in attention deficit/hyperactivity disorder. Biol Psychiatry 46:1690–1697

Buckley T and Schatzberg A. 2005. Review: On the Interactions of the Hypothalamic-Pituitary -Adrenal Axis (HPA) and sleep: Normal HPA Axis Activity and Circadian Rhythm, Exemplary Sleep Disorders. The Journal of Clinical Epidemiology & Metabolism 90(5): 3106 -3114.

Cadman T, Findon J, Eklund H, Hayward H, Howley D, Cheung C et al. Six-year follow-up study of combined type ADHD from childhood to young adulthood: Predictors of functional impairment and comorbid symptoms. Eur Psychiatry, 2016;35: 47-54

Cajochen C, Frey S, Anders D, Späti J, Bues M, Pross A, Mager R, Wirz-Justice A, Stefani O. Evening exposure to a light-emitting diodes (LED)-backlit computer screen affects circadian physiology and cognitive performance. J Appl Physiol 110: 1432–1438, 2011. First published March 17, 2011; doi:10.1152/japplphysiol.00165.2011.

Chio V, Schenk J.(2012). Mechanisms of action of methamphetamine within the catecholamine and serotonin areas of the central nervous system. Curr Drug Abuse Rev 5:227-242

Clarke, A. R., Barry, R. J., McCarthy, R., & Selikowitz, M. (1998). EEG analysis in attention-deficit/hyperactivity disorder: A comparative study of two subtypes. Psychiatry Research, 81, 19-29.

Coogan A and McGowan N. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. 2017. ADHD attention deficit and hyperactivity disorder. ADHD Attention Deficit and Hyperactivity Disorders 9(3). DOI: 10.1007/s12402-01600214-5

Corkum P, Lingkey-Pottie P, Davidson F et al. BetterNights/Better Days – Distance Intervention for Insomnia in School-Aged Children with/Without ADHD: A Randomized controlled Trial. 2016. Journal of Paediatric Psychology 41(6):jsw031. DOI: 10.1093/jpepsy/jsw031

Cortoos A, De Valck E, Arns M, et al. An exploratory study on the effects of tele-neurofeedback and tele-biofeedback on objective and subjective sleep patients with primary insomnia. Appl Psychophysiol Biofeedback. 2010;46:188-197

Custers K, Van den Bulck J. (2012). Television viewing, internet use and self reported bedtime and rise time in adults: implications for sleep hygiene recommendations from an exporatory cross-sectional study. Behjavoural Sleep Medicine, 10(2), 96-105.

De Gennaro L., Ferrara M. (2003). Sleep spindles: an overview. Sleep Med. Rev. 7, 423–440. 10.1053/smrv.2002.0252

De Lecea L and Huerta R. Hypocretin (orexin) regulation of sleep-to-wake transitions. Frontiers in Pharmacology. February 2014; Volume 5. Article 16

De Lecea L, Carter M and Adamantidis A. Shining Light in Wakefulness and Arousal. Biol Psychiatry. 2012 June 15; 71(12): 1046-1052

De Lecea L. Hypocretins and the neurobiology of sleep-wake mechanisms. Prog Brain Res. 2012: 198: 15-24

Diaz-Roman A, Mitchell R, Cortese S. Sleep in adults with ADHD: Systematic review and meta-analysis of subjective and objective studies. Neurosci Biobehav Rev. 2018. Feb 22 SO149-7634/187; 30013-7

Ding Y, Grady D et al., 2002 – Evidence of positive selection acting at the human dopamine receptor D4 gene. Proc Natl Acad Sci USA. 2002, Jan8; 99(1):309-14

Dijk D, Roth C, Landolt H, Werth E, Aeppli M, Achermann P et al. (1995). Melatonin effect on daytime sleep in men: suppression of EEG low frequency activity and enhancement of spindle frequency activity. Neurosci Lett. 201, 13-16

Doran AR, Labarca R, Wolkowitz OM, Roy A, Douillet P, Pickar D. Circadian variation of plasma homovanillic acid levels is attenuated by fluphenazine in patients with schizophrenia. Arch Gen Psychiatry. 1990;47:558-63. Met opmaak: Engels (V.S.)

Eban-Rothschild, Giardino W and de Lecea L. To sleep or not to sleep: neuronal and ecological insights. Curr Opin Neurobiol. 2017. Jun:44:132-138

Figueiro M, Plitnick B, Rea M. Pulsing blue light through closed eyelids: effects on acute melatonin suppression and phase shifting of dim light melatonin onset. Nat Sci Sleep. 2014; 6: 149-156. doi: 10.2147/NSS.S73856

González S, Moreno-Delgado D, Moreno E, Pérez-Capote K, Franco R, et al. Circadian- Related Heteromerization of Adrenergic and Dopamine D4 Receptors Modulates Melatonin Synthesis and Release in the Pineal Gland. (2012) Circadian-Related Heteromerization of Adrenergic and Dopamine D4 Receptors Modulates Melatonin Synthesis and Release in the Pineal Gland. PLOS Biology 10(6): e1001347. https://doi.org/10.1371/journal.pbio.1001347

Granet DB, Gomi CF, Ventura R, Miller-Scholte A. The relationship between convergence insufficiency and ADHD. Strabismus. 2005;13:163-8.

Green CB, Besharse JC. Retinal circadian clocks and control of retinal physiology. J Biol Rhythms. 2004;19:91-102.

Gregory A, Agnew-Blais J, Matthews T, Moffitt T, Arseneault L. ADHD and Sleep Quality: Longitudinal Analyses from Childhood to Early Adulthood in a Twin Cohort. J Clin Child Adolesc Psychol. 2017;46:284-94

Gronlund MA, Aring E, Landgren M, Hellstrom A. Visual function and ocular features in children and adolescents with attention deficit hyperactivity disorder, with and without treatment with stimulants.Eye (Lond) 2007;21:494-502.

Hegerl U, Hensch T. The vigilance regulation model of affective disorders and ADHD. Neurosci Biobehav Rev. 2014;44:45-57.:10.1016/j.neubiorev.2012.10.008. Epub Oct 22.

Hoebert M, Heijden KB, Geijlswijk IM, Smits MG. Long-term follow-up of melatonin treatment in children with ADHD and chronic sleep onset insomnia. J Pineal Res. 2009;47:1–7. doi: 10.1111/j.1600-079X.2009.00681.x.

Hoedlmoser K, Pecherstorfer T, Gruber G, Anderer P, Doppelmayr M, Klimesch W et al. (2008). Instrumental conditioning of human sensorimotor rhythm (12-15hz) and its impact on sleep as well as declarative learning. Sleep 31, 1401-1408

Honma K, Honma S. (2009). The SCN-independent clocks, methamphetamine and food restriction. Eur J Neurosci 30: 1707-1717

Huang MC, Ho CW, Chen CH, Liu SC, Chen CC, Leu SJ. Reduced expression of circadian clock genes in male alcoholic patients. Alcohol Clin Exp Res. 2010;34:1899–1904.

Huang YS, Guilleminault C, Li HY, Yang CM, Wu YY, and Chen NH. 2007. Attention-deficit/hyperactivity disorder with obstructive sleep apnea: a treatment outcome study. Sleep Med. 8(1):18-30

Hubbard J, Ruppert E, Gropp C, Bourgin p. Non-circadian direct effects of light on sleep and alertness: Lesson from transgenic mouse models. Sleep Med. Rev. 2013; 17: 445-452

Iuvone PM, Galli CL, Garrison-Gund CK, Neff NH. Light stimulates tyrosine hydroxylase activity and dopamine synthesis in retinal amacrine neurons. Science. 1978;202:901-2.

Iuvone PM, Tosini G, Pozdeyev N, Haque R, Klein DC, Chaurasia SS. Circadian clocks, clock networks, arylalkylamine N-acetyltransferase, and melatonin in the retina. Progress in retinal and eye research. 2005;24:433-56.

Jackson CR, Ruan GX, Aseem F, Abey J, Gamble K, Stanwood G, Palmiter RD, Iuvone PM, McMahon DG. Retinal dopamine mediates multiple dimensions of light-adapted vision. J Neurosci. 2012;32:9359–9368. doi: 10.1523/JNEUROSCI.0711-12.2012

Johnstone, S. J., Tardif, H. P., Barry, R. J., & Sands, T. (2001). Nasal bilevel positive airway pressure therapy in children with a sleep-related breathing disorder and attention-deficit hyperactivity disorder: Effects on electrophysiological measures of brain function. Sleep Medicine, 2(5), 407-416. doi:10.1016/S1389-9457(01)00121-6

Konofal E, Lecendreu M, Cortese S. Sleep and ADHD. Sleep Medicine (2010); 652-658

Kooji J and Bijlenga D. High prevalence of Self-Reported Photophobia in Adult ADHD. Front Neurol. 2014; 5:256

Kim J, Bailey M, Weller J, Sugden D, Rath M, Meller M, & Klein D. (2010). Thyroid hormone and adrenergic signalling interact to control pineal expression of the dopamine receptor D4 gene (drd4). Molecular and Cellular Endocrinology, 314, 128-135.

Kim S, Chen S, Tannock R. Visual function and color vision in adults with Attention-Deficit/Hyperactivity Disorder. Journal of Optometry. 2014;7:22-36.

Kurth S, Dean D, Achermann P, O'Muircheartaigh J, Huber R, Deoni S et al. Increased Sleep Depth in Developing Neural Networks: New Insights from Sleep Restriction in Children. Front Hum Neurosci. 2016;10:456.

Langberg J, Molitor S, Oddo L, Eadeh H, Dvorsky M, Becker S. Prevalence, Patterns and Predictors of Sleep Problems and Daytime Sleepiness in young adolescents with ADHD. J Atten Disord. 2017:1087054717690810.

Lui X. 2004. Sleep and adolescent suicidal behaviour. Sleep 27(7): 1352-1358

Martin L, Aring E, Landgren M, Hellstrom A, Andersson Gronlund M. Visual fields in children with attention-deficit / hyperactivity disorder before and after treatment with stimulants. Acta Ophthalmol (Oxf). 2008;86:259-64.

Matricciani L, Olds T, Petkov J. In search of lost sleep: secular trends in the sleep time of school-aged children and adolescents. Sleep Med Rev. 2012;16(3):203–211.

McGowan N and Coogan A. Sleep and circadian rhythm function and trait impulsivity.: An actigraphy study. Psychiatry Res. 2018;268:251-6

Mendoza J, Challet E. Circadian insights into dopamine mechanisms. Neuroscience. 2014;282:230-42.

Mezer E, Wygnanski-Jaffe T. Do children and adolescents with attention deficit hyperactivity disorder have ocular abnormalities? European journal of ophthalmology. 2012;22:931-5.

Molina B, Henshaw S, Swanson J, Arnold L , Vitiello B, et al. The MTA at 8 Years: Prospective Follow-Up of Children Treated for Combined Type ADHD in a Multisite Study. J Am Acad Child Adolesc Psychiatry. 2009 May ; 48(5): 484–500. doi:10.1097/CHI.0b013e31819c23d0.

Morash-Conway J, Gendron M, Corkum P. The role of sleep quality and quantity in moderating the effectiveness of medication in the treatment of children with ADHD. Atten Defic Hyperact Disord. 2017;9:31-8. doi: 10.1007/s12402-016-0204-7. Epub 2016 Aug 11.

Mundey K, Benloucif S, Harsanyi K, Dubocovich ML, Zee PC. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. Sleep. 2005;28:1271-8.

Nikolaidis A, Gray JR. ADHD and the DRD4 exon III 7-repeat polymorphism: an international meta-analysis. Social cognitive and affective neuroscience. 2010;5:188-93.

O'Brien L. The neurocognitive effects of sleep disruption in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2009;813-23

Olbrich S, van Dinteren R and Arns M. Personalized Medicine: Review and Perspectives of Promising Baseline EEG Biomarkers in Major Depressive Disorder and Attention Deficit Hyperactivity Disorder. Neuropsychobiology 2015;72:229–240 DOI: 10.1159/000437435

Owens JA, Belon K, Moss P. Impact of delaying school start time on adolescent sleep, mood, and behaviour. Arch Pediatr Adolesc Med. 2010;164:608-14.

Palma J, Urrestarazu E, Alegre M et al. (2103). Cadiac autonomic impairment during sleep is linked with disease severity in Parkinson's Disease. Clin Neurophysiol 124:1163-1168

Parekh PK, Ozburn AR, McClung CA. Circadian clock genes: effects on dopamine, reward and addiction. Alcohol. 2015;49:341-9.

Parekh PK, Ozburn AR, McClung CA: Circadian clock genes: effects on dopamine, reward and addiction. Alcohol. 2015;49(4):341–9. 10.1016/j.alcohol.2014.09.034

Raymond, R.C., Warren, M., Morris, R.W., and Leikin, J.B. (1992) Periodicity of presentations of drugs of abuse and overdose in an emergency department. J. Toxicol. Clin. Toxicol. 30, 467–478.

Roenneberg T and Merrow M. The Circadian Clock and Human Health. Current Biology 26, R432-R443, May 23, 2016

Roybal, K., Theobold, D., Graham, A., DiNieri, J.A., Russo, S.J., Krishnan, V., Chakravarty, S., Peevey, J., Oehrlein, N., Birnbaum, S., et al. (2007). Mania-like behavior induced by disruption of CLOCK. Proc. Natl. Acad. Sci. USA 104, 6406–6411

Ruan G-X, Zhang D-Q et al. Circadian organization of the mammalian retina. PNAS; June 20, 2006. Vol 103, No 25. 9703-9708.

Rybak Y, McNeely H, Mackenzie B, Jain U, Levitan R. 2006. An open trial of light therapy in adult attention deficit /hyperactivity disorder. Journal of Clinical Psychiatry. 67, 1527-1535.

Saletin, J. M., Coon, W. G., & Carskadon, M. A. (2017). Stage 2 sleep EEG sigma activity and motor learning in childhood ADHD: A pilot study. Journal of Clinical Child and Adolescent Psychology : The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53, 46(2), 188-197. doi:10.1080/15374416.2016.1157756

Sander C, Arns M, Olbrich S, Hegerl U. EEG-Vigilance and response to stimulants in paediatric patients with attention deficit/hyperactivity disorder. Clinical Neurophysiology. 2010;121:1511–1518. doi: 10.1016/j.clinph.2010.03.021

Santisteban JA, Stein MA, Bergmame L, Gruber R. Effect of extended-release dexmethylphenidate and mixed amphetamine salts on sleep: a double-blind,randomized, crossover study in youth with attention-deficit hyperactivity disorder. CNS Drugs. 2014;28:825-33.

Schmidt T, Kofuji P. Functional and morphological differences among intrinsically photosensitive retinal ganglion cells. J. Neurosci. 2009 Jan 14: 29(2); 476-482

Sciberras E, DePetro A, Mensah F, Hiscock H. Association between sleep and working memory in children with ADHD: a cross sectional study. Sleep Med. 2015; 16:1192-7

Sedky, K., Bennett, D. S., & Carvalho, K. S. (2014). Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: A meta-analysis. Sleep Medicine Reviews, 18(4), 349-56. doi:10.1016/j.smrv.2013.12.003

Silvestri R, Gagliano A, Aricò I, Calarese T, Cedro C, Bruni O, Condurso R, Germanò E, Gervasi G, Siracusano R, Vita G & Bramanti P. (2009). Sleep disorders in children with Attention-Deficit/Hyperactivity Disorder (ADHD) recorded overnight by video polysomnography. Sleep Medicine, Vol.10, No.10, (Dec 2009), pp.1132-8

Sinha S. 2011. Basic mechanisms of sleep and epilepsy. Journal of Clinical Neuro-physiology. 28, 103-110

Stone RA, Pardue MT, Iuvone PM, Khurana TS. Pharmacology of myopia and potential role for intrinsic retinal circadian rhythms. Experimental eye research.2013;114:35-47.

Tosini G, Baba K, Hwang C and Iuvone P. Melatonin: An Underappreciated Player in Retinal Physiology. Exp Eye Res 2012. 103: 82-89

Uz T, Arslan A, Kurtunca M, etal. (2005). The regional and cellular expression profile of the melatonin receptor MT1 in the central dopaminergic system. Brain Res Mol Brain Res 136:45-53.

Van den Bulck J (2004) Television viewing, computer game playing, and internet use and self-reported time to bed and time out of bed in secondary-school children. Sleep 27(1):101–104

Van der Heijden KB, Smits MG, Van Someren EJW, Gunning WB. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. Chronobiol Int. 2005;22:559-70.

Van der Heijden KB, Smits MG, Van Someren EJW, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. J Am Acad Child Adolesc Psychiatry. 2007;46:233-41.

Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: Dose-response effects on neurobiological functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2003, March 15;26(2): 117-126

Van Dongen, H. P. A., Baynard, M. D., Maislin, G., & Dinges, D. F. (2004). Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. Sleep, 27(3), 423-33.

Van Doren J. Arns M, Heinricj H, Vollebregt M, Strehl U, Loos S. Sustained effects of neurofeedback in ADHD: a systematic review and meta-analysis. European Child & Adolescent Psychiatry. 2018. https://doi.org/10.1007/s00787-018-1121-4

Van Veen MM, Kooij JJS, Boonstra AM, Gordijn MCM, Van Someren EJW. Delayed circadian rhythm in adults with attention-deficit/hyperactivity disorder and chronic sleep-onset insomnia. Biol Psychiatry. 2010;67:1091-6.

Videnovic A and Golombek D. Circadian and sleep disorders in Parkinson's Disease. Exp. Neurol. 2013 May; 243:45-56

Vollebregt M, Arns M, Monastra V, Roley-Roberts M, Arnold E, Hollway J. Shedding light on the aetiology of ADHD: The influence of disturbed sleep on symptomatology. Manuscript under review.