Altered Circadian Profiles in Attention Deficit/Hyperactivity Disorder:

An Integrative Review and Theoretical Framework for Future Studies

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Abbreviations

APA	American psychiatric association
ADHD	attention-deficit hyperactivity disorder
SCN	suprachiasmatic nucleus
CLOCK gene	circadian locomotor output cycles kaput gene
LC	locus coeruleus
MSLT	multiple sleep latency test
PSG	polysomnography
ODD	oppositional defiant disorder
CD	conduct disorder
CBCL	child behavior checklist
MEQ	morningness-eveningness questionnaire
SOI	sleep onset insomnia
DLMO	dim light melatonin onset
HPA axis	hypothalamic-pituitary-adrenal axis
CRF	corticotropin releasing factor
RAS	reticular activation system
DMH	dorsomedial hypothalamic nucleus
VLPO area	sleep-related ventrolateral preoptic area
NE	noradrenaline
PFC	prefrontal cortex
DRD-4 gene	dopamine receptor D_4 gene
fMRI	functional magnetic resonance imaging
PET	positron emission tomography
EEG	electroencephalogram
ERP	event related potential

Abstract

Disruptions in the sleep-wake cycle and the circadian system have been found in a wide range of psychiatric disorders and are generally correlated with clinical severity and diminished quality of life. Emerging evidence suggests similar disturbances may be found in attention deficit/hyperactivity disorder (ADHD). Here we review the available literature on across the day fluctuations in ADHD-related processes in terms of ; (i) time of day effects on behavior and activity; (ii) *morningness-eveningness* chronotypology; (iii) sleep/wake rhythms; and (iv) rhythmicity in neuroendocrine and neurophysiological responsiveness. On this basis, we propose a neurobiological framework to guide future study, which sees circadian effects in ADHD, along with other aspects of ADHD arousal-related deficits (e.g., cognitive energetic deficits), as being the result of dysregulated locus coeruleus function. Based on this perspective specific recommendations for future research are presented.

Keywords: ADHD, arousal, circadian, suprachiasmatic nucleus, eveningness, behavior, sleep, melatonin, cortisol, heart rate, locus coeruleus

1. Introduction

There is mounting evidence to support the notion that circadian rhythms are altered in a wide range of psychiatric diseases, especially affective disorders (see for reviews: Boivin, 2000; Germain and Kupfer, 2008; McClung, 2007; Wirz-Justice, 2006). For example, impaired sleep and daytime fatigue are included in the diagnostic criteria for depressive disorders (American Psychiatric Association, APA, 2000) where diurnal variations in symptoms (e.g., mood and psychomotor activity) have frequently been reported. These fluctuations are reflected in physiological measures such that, compared to a control population, depressive patients show alterations in circadian rhythms of melatonin and (Pacchierotti et al., 2001) cortisol levels (Deuschle et al., 1997); body temperature (Daimon et al., 1992); and heart rate (Stampfer, 1998). Moreover, some interventions that change the timing of the biological clock in the brain (e.g., sleep deprivation, light therapy) have efficacy as treatments for these conditions (Wehr et al., 1979). For instance, Agomelatine, a new antidepressive agent with phase advancing characteristics has become available (Fornaro et al., 2010; San and Arranz, 2008) and appears to be effective in at least a subgroup of patients (Duke, 2008). Diurnal variations in symptoms and altered profiles of circadian markers are also found in seasonal depressive disorder (Lewy et al., 2006), bipolar disorder (Harvey, 2008), and schizophrenia (Rao et al., 1994).

In attention deficit/hyperactivity disorder (ADHD) it is well established that behavioral symptoms and performance fluctuate both spontaneously over time and in response to changing environmental contexts (Antrop et al., 2005a; Luman et al., 2005; Power, 1992; Sonuga-Barke et al., 1996; Toplak and Tannock, 2005; Wiersema et al., 2006b; Zentall and Zentall, 1976). In clinical practice, sleep-wake problems are frequently reported by individuals with ADHD or their parents, even though these problems are not currently included in the diagnostic criteria. As disruptions of circadian rhythms and sleep-wake cycles

are generally expected to have a significant impact on symptom severity (Fallone et al., 2001), daytime functioning (Bearpark and Michie, 1987), and health outcomes (Gangwisch, 2009; Scheer et al., 2009), in recent years, researchers have become increasingly interested in the possibility that such effects are implicated in ADHD pathophysiology. Gathering knowledge on diurnal variations in ADHD is important as these results may improve educational guidelines (such as optimal timing of academic lessons) and diagnostic and therapeutic assessments. For example, knowledge of time of day effects could lead to the adjustment of dosing and timing of ADHD medication to optimally observe and treat problematic behavior at a particular time of day. Furthermore, if findings on disrupted circadian rhythms are confirmed in ADHD, they may point to the value of circadian-based therapies in ADHD such as melatonin treatment and light therapy. To the best of our knowledge, there is no review that assesses findings on circadian effects in ADHD.

To date, the underlying mechanisms of circadian rhythm alterations in psychiatric disorders in general, or in some of these conditions specifically, are still unknown. The suprachiasmatic nucleus (SCN) in the ventral hypothalamus (Weaver, 1998) is thought to drive these 24-hour fluctuations in both physiological (e.g., body temperature, heart rate, hormone secretion) and psychological (cognitive performance, personality and behavior) functions (Carrier and Monk, 2000; Haus, 2007; Hofstra and de Weerd, 2008; Tankova et al., 1994; Young, 2006). This biological clock has an endogenous nature - rhythms persist even in the absence of external, environmental information. However, exogenous cues, also called zeitgebers (e.g., light, but also sleep deprivation and social cues), tune this clock to a specific rhythm. The SCN is responsible for the functional time synchronization of all peripheral oscillators found in cells, tissues, and organs. Communication to peripheral structures takes place through both neural and endocrine factors, and enhances synchronized functioning of different human systems, including the central nervous system, the autonomic nervous system,

and the endocrine tissues (Haus, 2007). The sleep-wake cycle is also regulated by the SCN. However, this circadian process (process C) interacts with a homeostatic process (process S) to maintain wakefulness (which we further refer to as arousal; a physiological and psychological state of being awake, aware, and alert) during the day and to consolidate sleep at night. Whereas the process C is particularly important in the timing of sleep and arousal states, the process S regulates the duration and structure of sleep (Borbély, 1982). When considering the available evidence, disruptions in circadian rhythms and sleep-wake cycles have usually been related to changes in the timing of the biological clock (though alternative hypotheses have been provided; e.g., social zeitgeber theory, process S deficiency; Boivin, 2000; Grandin et al., 2006). Alterations in biological clock timing have been seen as a consequence of changes in neurotransmitter activity related to the condition (Maurizi, 1984; Pacchierotti et al., 2001), but there is emerging research on circadian locomotor output cycles kaput (CLOCK) genes as an etiological factor (Barnard and Nolan, 2008).

The current paper has two aims. First, to *systematically review published data on across the day fluctuations in ADHD behavior, performance and physiological functioning* in terms of ; (i) morningness-eveningness chronotypology; (ii) time of day effects of behavior and activity; (iii) sleep/wake rhythm problems; and (iv) rhythmicity in neuroendocrine and neurophysiological factors. Clinical implications of these (putative) effects will also be drawn out. Second, to *develop a neurobiological framework to guide future research into circadian disruptions in ADHD*. At the heart of this account is the hypothesis that disrupted circadian rhythms in ADHD, along with other arousal-related processes thought to be deficient in ADHD such as cognitive energetic problems, are due to locus coeruleus (LC) dysfunction.

2. Review of Circadian Profiles in ADHD

ADHD is one of the most prevalent psychiatric disorders in children and adolescents (Spencer et al., 2007), characterized by persistent problems in attention, hyperactivity and

impulsivity (APA, 2000). Based on the symptomatology, different ADHD subtypes can be distinguished namely the inattentive type, the hyperactive-impulsive type, and the combined (inattentive and hyperactive-impulsive) type. Although pervasiveness and persistence of symptoms and impairment are important criteria for the diagnosis of ADHD (APA, 2000), time- and context-dependent variability in behavioral symptoms and performance has been reported (Antrop et al., 2005a; Luman et al., 2005; Power, 1992; Sonuga-Barke et al., 1996; Toplak and Tannock, 2005; Wiersema et al., 2006b; Zentall and Zentall, 1976). Fluctuations in ADHD behavior have typically been explained in terms of either context-dependent acute changes in arousal state (both hypo- and hyperarousal; see section 3.2 and 3.3 for more detailed information), which in turn have been thought to display spontaneous circadian effects across the day (see section 3.1 and 3.4 for more detailed information).

2.1. Method

An electronic literature search was performed using Web of Science and Pubmed (Medline) databases. Search terms were "circadian" or "diurnal" or "time of day" intersected with "ADHD" or "hyperactivity". Based on the results of these strings, a more specific search was conducted using all combinations of previous terms with "eveningness" or "physical activity" or "sleep" or "melatonin" or "cortisol" or "heart rate". A search through the references of original and related articles resulted in additional citations. Searches were restricted to papers in the English language published from 1967 to the present and included all studies with children, adolescents, and adults as participants. Since the "sleep" search string generated a lot of original articles and reviews, this paper focuses on findings with high relevance to the sleep-wake 'rhythm', i.e. results on sleep duration, sleep latency, and sleep efficiency as obtained by subjective and objective evaluation. The latter comprises investigations using either actigraph or multiple sleep latency test (MSTL). Polysomnography (PSG) research mainly focusing on sleep 'architecture', e.g. REM and non-REM, and ADHD

has been thoroughly reviewed elsewhere (Cohen-Zion and Ancoli-Israel, 2004; Cortese et al., 2009; Cortese et al., 2006; Sadeh et al., 2006) and is not reviewed again here.

Because the literature directly related to circadian measures and ADHD is limited, studies using a single or short-term basal measurement of a circadian endocrine or autonomic variable were also included, even if they did not examine complete circadian patterns. However, studies including a basal pre-test measurement in the context of an experimental task were deemed to be less relevant for this review: These measurements could be influenced by anticipatory stress and have therefore only limited value in circadian evaluations. Time of day effects reported in behavioral studies were also considered, even if these primarily focused on contextual factors and not on 24-hour fluctuations. In addition, studies in patients with ADHD and comorbid disorders such as insomnia or disruptive behavioral disorders (i.e., oppositional defiant disorder (ODD) or conduct disorder (CD)) were reviewed although it is often difficult to disentangle the effects of the comorbid disorders from ADHD itself.

2.2. Results

The searches yielded studies using both subjective (e.g., questionnaires on chronotypology and sleep) and objective (e.g., endocrine measures, activity, and physiological registration) dependent measures. The majority of studies evaluated circadian rhythms in a naturalistic setting.

2.2.1. Chronotypology.

Chronotypology refers to a continuum on which individuals can be rated from *high morning* to *high evening* types (Cavallera and Giudici, 2008; Kerkhof, 1985; Tankova et al., 1994). The *morningness-eveningness* paradigm correlates highly with circadian rhythms and physiological measures of arousal (Baehr et al., 2000; Jankowski and Ciarkowska, 2008). We identified one paper in a general population of children and three papers in a clinical sample of adults with ADHD addressing this issue. In a healthy child population aged 8-13, Susman

et al. (2007) described an association between ADHD symptoms and distinctive patterns of

circadian preference. The authors reported *eveningness* to be associated with higher scores on

both attention problems and rule-breaking behavior in boys as measured by the *Child*

Behavior Checklist (CBCL; Achenbach, 2001). In a clinical population of adults with ADHD,

Rybak et al. (2007) found a circadian phase delay during the fall/winter period in adults with

ADHD: They reported *eveningness*, as measured by the *morningness-eveningness*

questionnaire (MEQ) (Horne and Ostberg, 1976), to correlate with both subjective (Brown

Adult Attention Deficit Disorder Scale; Brown, 1996) and objective (Conners' Continuous

Performance Test; Conners, 2000) measures of attention deficits in ADHD. The association

between *eveningness* and ADHD appeared to be independent of comorbid seasonal affective

disorder. Caci et al. (2009) confirmed this relationship in adults suspected of having ADHD.

Although inattention symptoms were strongly related to *eveningness* in their study,

impulsivity and hyperactivity were not. Therefore, the authors suggested that *eveningness*

may constitute an endophenotype of the predominantly inattentive subtype of ADHD. Also

Bae et al. (2010) supported the idea that *eveningness* may be strongly associated with

inattention problems in adult ADHD. Considering hyperactivity and impulsivity, they

reported an association with *eveningness* in male subjects only. The link between ADHD and

a later time of day preference (i.e., *eveningness*) is thought to reflect a delayed timing of

optimal arousal levels. One possibility is that this differential across the day arousal pattern in

ADHD is due to an altered 24-hour rhythmic control of the biological clock.

2.2.2. Diurnal variations in behavior and performance.

Behavioral observational research has provided overwhelming evidence for significant

group differences between ADHD and controls in terms of mean levels of attention and

activity measured across long periods of time. Although fluctuations in ADHD

symptomatology and performance have been well studied in relation to changing

environmental demands (Antrop et al., 2005a; Luman et al., 2005; Power, 1992; Sonuga-Barke et al., 1996; Toplak and Tannock, 2005; Wiersema et al., 2006b; Zentall and Zentall, 1976), only seven studies have looked systematically at time of day effects (Table 1).

<center>**<INSERT TABLE 1 ABOUT HERE>**</center>

Observational studies: Zagar and Bowers (1983) reported a relationship between the hyperactive behavior of children with ADHD and time of day. During their observations (repeated 4-min periods once a week across four weeks), the authors found children with ADHD to be more inattentive and active in the afternoon. Recently, also Wehmeier et al. (2011) reported that the degree to which the various times of the day are found to be challenging fluctuates over the day. The authors investigated performance across different times of the day in children with ADHD receiving placebo or atomoxetine treatment. Though they found no indication of a differential treatment effect of the day, both groups showed a peak performance at 10 am which was followed by a decline with a trough at 2 pm; then performance improved again at 5 pm and declined toward the evening hours. The two studies described above could however not disentangle these findings from daily rhythms in attention (Lawrence and Stanford, 1999) and activity (Riddoch et al., 2007) in the normal population because they did not include a control group. Antrop et al. (2005b) investigated the influence of time of day on the effects of playtime on behavior in elementary school children with ADHD and normal developing classmates. They found an increase in hyperactive behavior in ADHD children only in the afternoon after controlling for several factors such as medication (see Table 1).

Actigraph research: Analysis of activity in terms of its relative/absolute intensity has revealed distinctive time of day effects in ADHD. Porrino et al. (1983) registered naturalistic activity levels in children with ADHD and control children during seven consecutive days. They reported that children with ADHD were more active than control children only during

specific hours of the school day (7 am, 8 am, 10 am, 11 am, noon, 2 pm, 3 pm, and 5 pm).

However, the sample size in their study was small and direct observations were not performed.

The authors tried to overcome this problem by keeping a diary of the children's activities.

They discovered that the hours of increased activity in children with ADHD coincided with

structured school activities (reading and math classes), but not with recess/lunch periods. Also

Tsujii et al. (2007) pointed to the possibility that time of day effects are likely to be

confounded by context effects. They investigated the level of activity in different naturalistic

educational settings, e.g., structured in-seat classes and non-structured classes at different

times of day. Children with ADHD were significantly more active than controls during

structured in-seat lessons in the afternoon, but no group differences were found during non-

structured classes, or during morning classes. More recently, Licht and Tryon (2009) found a

significant group x time of day interaction effect in their naturalistic study investigating

activity levels in a small group of children with ADHD and controls during one week. As

hyperactivity in the ADHD group was only obvious during daytime and not during nighttime

periods, the authors suggested that -along with contextual factors- circadian rhythms might

play a role in these differential activity patterns. Similar findings were obtained in a larger

sample by Imeraj et al. (2011). Moreover, their finding of higher daytime activity levels -

especially during noon and early afternoon hours- confirmed an important role for time of day

effects in addition to environmental conditions in the expression of (afternoon) problem

behavior in ADHD.

2.2.3. Sleep-wake rhythms.

Ten reviews on sleep patterns and ADHD in children and adults have already been

published (Cohen-Zion and Ancoli-Israel, 2004; Cortese et al., 2009; Cortese et al., 2006;

Gruber, 2009; Owens et al., 2009; Owens, 2005; Philipsen et al., 2006; Sadeh et al., 2006; van

der Heijden et al., 2005a; Walters et al., 2008). In general, sleep studies in ADHD have given

mixed results on both subjective (i.e., clinical history, sleep diaries, and rating scales) and objective (i.e., actigraphy, and MSTL) sleep measures. The presence of different confounding factors in different studies have been suggested to be responsible for some of these discrepancies, e.g., age and sex (Boonstra et al., 2007), seasonal effects (Boonstra et al., 2007), temporal changes in DSM classification (Cortese et al., 2006), ADHD subtype (Wiggs et al., 2005), medication status (Corkum et al., 1999; Cortese et al., 2006), and psychiatric comorbidity (Corkum et al., 1999; Cortese et al., 2006). The relation between ADHD and sleep becomes even more complex as sleep-related disorders such as restless leg syndrome and sleep apnea can present alongside ADHD (van der Heijden et al., 2005a). Primary sleep disorders may be a true comorbid condition with idiopathic ADHD, but some children may actually have a primary sleep disorder, misdiagnosed as ADHD, due to the fact that diurnal manifestations of primary sleep disorders can mimic ADHD symptoms (Chervin et al., 2002; Cortese et al., 2005). As this review focuses on the effect of circadian rhythms in ADHD, we concentrate here on circadian characteristics of the sleep-wake cycle, i.e., time of falling asleep, time of awakening, disturbed sleep phases, and daytime sleepiness, in children and adults with ADHD. As the timing of the sleep-wake cycle is controlled by the circadian pacemaker (i.e., the process C; Borbély, 1982), alterations in the timing of sleep and awakening could reflect an underlying circadian shift of the biological clock. Such disruption can cause significant daytime sleepiness, which is hypothesized to be more pronounced earlier in the day. However, daytime sleepiness and nighttime awakening could also reflect problems in the arousal-sleep "flip-flop" mechanism pointing to instability of the transition between sleep and wake, not necessarily related to specific times of day (Schwartz and Roth, 2008). For an overview of the 26 subjective and objective original papers included, see Table 2.

\<INSERT TABLE 2 ABOUT HERE\>

Subjective evaluations: Nighttime parameters with high relevance to the sleep-wake rhythm include sleep onset, sleep duration, nighttime awakenings and difficulties with morning awakenings. Considering sleep onset difficulties and sleep onset latency, some studies report that children with ADHD show more difficulties initiating sleep or have longer sleep onset latency than normal controls (Hvolby et al., 2009; O'Brien et al., 2003a; O'Brien et al., 2003b; Owens et al., 2000), whereas other studies report sleep onset problems to be associated with ODD comorbidity and stimulant medication rather than ADHD itself (Corkum et al., 1999; Mick et al., 2000). Higher bedtime resistance in an ADHD population with ODD may exacerbate sleep complaints. However, an added effect of comorbid ODD on problematic behavior scores around bedtime was not confirmed by the study of Hvolby et al. (2009). As Owens et al. (2000) included unmedicated children with ADHD, stimulant medication could not be responsible for sleep onset latency problems reported in their study. With respect to total sleep duration, some authors reported no differences in sleep duration considering clinical samples of children with ADHD and normal controls (Hvolby et al., 2009; Marcotte et al., 1998; Mick et al., 2000), in contrast to other authors who reported both longer (Corkum et al., 2001) and shorter (Owens et al., 2000) sleep duration in ADHD. Several recent studies in larger population samples confirmed that short sleep duration is associated with problems related to attentional control and hyperactivity/impulsivity (Paavonen et al., 2009; Pesonen et al., 2010; Touchette et al., 2009). In terms of sleep efficiency, some studies reported more nighttime awakenings in children with ADHD compared to normal controls (O'Brien et al., 2003a), whereas others found no differences (Hvolby et al., 2009; Mick et al., 2000). Although some authors described more difficulties with morning awakenings (Chiang et al., 2010; Corkum et al., 2001; Owens et al., 2009), others found no support for this (Corkum et al., 1999; Mick et al., 2000; O'Brien et al., 2003a). With regard to daytime parameters, excessive daytime sleepiness has consistently been found to be more common in

children with ADHD compared to normal controls (Chiang et al., 2010; Cortese et al., 2009; O'Brien et al., 2003a; O'Brien et al., 2003b; Owens et al., 2009; Owens et al., 2000). To date, there are few studies of adolescents and adults. In adolescence, subjective severity of sleep problems was related to stimulant medication and comorbid depressive symptoms (Stein et al., 2002), whereas in adults with ADHD, sleep problems such as sleep onset problems, difficulties with morning awakenings, and daytime sleepiness were reported to occur independent of stimulant medication and comorbidity (Schredl et al., 2007; Surman et al., 2009).

Objective evaluations: Actigraphy is a practical and accurate method to assess circadian rhythm disorders as actigraphic data can also be analyzed in terms of more general patterns of activity and rest as indicative of the sleep-wake cycle (Morgenthaler et al., 2007). Actigraphic studies in ADHD show mixed results (Cohen-Zion and Ancoli-Israel, 2004). Crabtree et al. (2003) found a delayed sleep onset in a group of children with ADHD referred to a sleep centre. As the authors included both medication treated and unmedicated children, results may be confounded by medication status. However, in unmedicated samples of children with ADHD (children discontinued medication or were medication naïve), shorter sleep duration (Owens et al., 2009) and longer sleep onset latency (Hvolby et al., 2008) have been confirmed as compared to controls. Nevertheless, sleep onset latencies have been shown to increase following stimulant medication in multiple (placebo-controlled) studies (Corkum et al., 2008; Ironside et al., 2010; Schwartz et al., 2004). For example, Barkley et al. (1990) found 15% of their subjects with ADHD experiencing insomnia during the placebo condition and more than 50% in the methylphenidate condition. Beneficial effects of medication on some aspects of sleep such as nighttime awakenings and parasomnias have also been reported (Kim et al., 2010).

Not all studies using objective measures have found differentiating sleep-wake results in ADHD (Corkum et al., 2001; Dagan et al., 1997; Gruber et al., 2000). One explanation for this inconsistency is that higher night-to-night variability accounts for similar mean sleep estimates in ADHD and control groups, despite the fact that standard deviations are significantly different between groups (Crabtree et al., 2003; Gruber et al., 2000; van der Heijden et al., 2005a). Another possibility is that sleep/wake findings are only applicable to a specific subgroup of children with ADHD as Van der Heijden et al. (2005b) reported different findings in ADHD with a comorbid sleep disorder and ADHD without sleep problems. A subgroup of children with ADHD and comorbid chronic sleep onset insomnia (SOI) disorder, compared to children with ADHD without sleep problems, showed a delayed sleep onset (on actigraphy) together with a delayed onset of the nocturnal melatonin peak (dim light melatonin onset, DLMO). As no control group was included in this study, one cannot be certain to what extent ADHD with or without SOI would differ from controls. Parallel findings have recently been obtained in adults with ADHD and SOI (significant differences between ADHD with and without SOI; Van Veen et al., 2010). However, the authors also included a normal control group from which both ADHD+SOI and ADHD-SOI differed in sleep onset latency and sleep efficiency. Similarly, Boonstra et al. (2007) reported that adults with ADHD (irrespective of SOI) take longer to fall asleep, have lower sleep efficiency, and shorter within-night periods of uninterrupted sleep compared to normal controls. It is possible that the biological clock influencing the timing of sleep-wake cycles is set to a later time in children with ADHD as compared to controls. The DLMO additionally reflects this delayed sleep timing. The use of melatonin as a marker for circadian evaluation and the effect of melatonin treatment to reset the circadian clock in ADHD are discussed below.

Two studies using the MSLT reported significantly more daytime sleepiness in children and adolescents with ADHD than in controls (Golan et al., 2004; Lecendreux et al.,

2000). This means that subjects with ADHD have shorter sleep onset latency during one or more daytime naps. Although children with ADHD were more sleepy throughout the day, Golan et al. (2004) observed the most severe sleepiness was in the morning (8 AM). This finding is consistent with a delayed circadian rhythm in ADHD. In a driving simulation experiment, similar results were obtained in adult drivers with ADHD: They were more susceptible to fatigue earlier in the day (Reimer et al., 2007).

Altogether, a majority of studies on sleep-wake rhythms support a delayed sleep phase syndrome, suggestive of a disruption of the 24-hour sleep/arousal control, in (at least a subgroup of) subjects with ADHD. Several factors may have confounded these results (see Table 2 for more detailed study-specific information). However, a recent meta-analysis by Cortese et al. (2009), controlling for medication status and comorbidity, confirmed more sleep onset difficulties, night awakenings, difficulties with morning awakenings, higher sleep onset latency and lower sleep efficiency in children with ADHD (irrespective of comorbid SOI diagnosis). These characteristics provide additional support for the hypothesis of a delayed sleep phase syndrome in ADHD. As this meta-analysis did not consider other confounding factors (e.g., comorbid anxiety or depression, stress, difficulty settling down), it needs to be further determined to what extent these problems are specific to ADHD (or at least to a subgroup of ADHD). To address these issues a transdiagnostic approach has been proposed in the treatment of insomnia across a variety of psychiatry disorders (Harvey et al., 2011). This approach could be especially useful in relation to ADHD given that SOI problems occur in up to 54% of ADHD cases affecting daily functioning and quality of life (Tjon Pian Gi et al., 2003).

2.2.4. Circadian effects on neuroendocrine and neurophysiological processes.

To date, research using neuroendocrine (e.g., cortisol) and neurophysiological (e.g., heart rate) measures in ADHD are mainly laboratory-based. However some data from more naturalistic studies measuring across the day changes is available.

2.2.4.1. Melatonin.

Melatonin is an interesting hormonal marker used in the evaluation of circadian rhythms which affects the circadian regulation of different biological functions, including the sleep-wake cycle. Melatonin production by the pineal gland and the retina occurs at night such that concentrations are very low during daytime, increase at nightfall (DLMO) and peak around 3-4 am (Haus, 2007). DLMO production is the most reliable marker of circadian phase position (Hofstra and de Weerd, 2008; Klerman et al., 2002; Van der Heijden et al., 2005b; see also Macchi and Bruce (2004), Claustrat et al. (2005), and Benloucif et al. (2008) for a more detailed description of melatonin regulation, secretion, and analysis).

Deviant melatonin levels have been related to several psychiatric disorders including depression, mania (Crasson et al., 2004; Kennedy et al., 1996), and seasonal affective disorder (Lewy et al., 2006). Very recently, Chaste et al. (2011) provided the first genetic ascertainment of defects in the melatonin pathway of patients with ADHD. Two studies have examined endogenous melatonin rhythms in children with ADHD and there is one study in adults (see also Table 2). Compared to control subjects, Nováková et al. (2011) did not report different 24-h melatonin profiles in their group of children with ADHD (6-12y). However, when considering younger and older subgroups separately, subtle developmental differences were revealed: i.e., in the oldest children with ADHD (10-12 y) only the onset, but not the offset, phase delayed with increasing age. In their group of children with ADHD (6-12 y), Van der Heijden et al. (2005b) reported that 73% of subjects met the criteria for sleep onset insomnia. Based on the measurements of activity levels and DLMO, they found evidence for a delayed sleep phase syndrome, i.e. longer sleep onset, later wake-up time, and delayed

DLMO (Nagtegaal et al., 1998), in their subgroup of children with ADHD and comorbid

chronic SOI compared to the group with ADHD without sleep problems. This has been

confirmed in adults with ADHD+SOI compared to adults with ADHD-SOI and normal

controls (Van Veen et al., 2010). The therapeutic use of exogenous melatonin (5 mg

melatonin in the evening), used to reset the timing function of the SCN, is associated with

advanced sleep onset and DLMO compared to placebo in children with idiopathic chronic

sleep-onset insomnia (Smits et al., 2001; Smits et al., 2003). Also in children with ADHD,

melatonin administration is considered to be an effective treatment of initial SOI (Bendz and

Scates, 2010). Significant improvement in sleep parameters such as sleep onset and sleep

onset latency were described in both non-stimulant treated (Hoebert et al., 2009; Van Der

Heijden et al., 2007) and stimulant treated (Tjon Pian Gi et al., 2003; Weiss et al., 2006)

children with ADHD and insomnia. Although melatonin resets the circadian timing system,

no effect of melatonin on daytime behavior symptoms could be observed in the study of Van

der Heijden et al. (2007). In contrast, parents stated that melatonin was not only effective for

sleep onset insomnia, but also for behavior problems in the 3-year follow-up assessment of

this sample (Hoebert et al., 2009).

2.2.4.2. Cortisol.

The hypothalamic-pituitary-adrenal (HPA) axis is also sensitive to time information

from the SCN (Haus, 2007), which is reflected in a typical diurnal cortisol pattern with a

trough (the nadir) around midnight. In normal subjects, cortisol concentrations gradually

increase 2 to 3 hours after bedtime, with a peak (the acrophase) 30 to 45 minutes after

awakening, i.e., the cortisol awakening response. Levels then decrease gradually to nighttime

concentrations (Buckley and Schatzberg, 2005; Edwards et al., 2001). Cortisol level in saliva

is a reliable peripheral measure of arousal (see also Levine et al. (2007) for a review on the

analysis of cortisol).

With respect to ADHD, cortisol levels have mostly been measured in response to stress (Hong et al., 2003; Randazzo et al., 2008; Shin and Lee, 2007; Snoek et al., 2004; van West et al., 2009), although a few attempts have been made to evaluate the influence of time of day. Although most of the stress response studies also describe basal cortisol levels on a single pre-stress measurement, results on this measure are inconsistent and have only limited value in the evaluation of diurnal cortisol patterns. Intra- and inter-day variability in individual cortisol patterns requires an evaluation using repeated cortisol measures across several days (Bartels et al., 2003; Edwards et al., 2001; Houtveen and de Geus, 2009; Schulz et al., 1997). To our knowledge, such an 'ideal' investigation has only been applied in one study (Imeraj et al., 2012). We therefore include studies with multiple measurements across one day (combined morning and basal sampling), but also studies including awakening or basal samples only. For an overview of the thirteen studies considered, see Table 3.

<div align="center">**<INSERT TABLE 3 ABOUT HERE>**</div>

Most studies of diurnal patterns of cortisol have found a relationship between ADHD symptoms and altered circadian cortisol patterns. Results are inconsistent however showing both hypo- and hyperarousal deviations at different time points. Considering studies with repeated measurements across one day, Kaneko et al. (1993) originally found a normal diurnal cortisol pattern in only 43.3 % of the children with ADHD, suggesting a dysregulation of the HPA axis in the majority of children. Though Pesonen et al. (2011) could not find an association beween ADHD symptoms and diurnal cortisol profile in 8-year old children from the general population, other authors did. In a slightly older population sample, Susman et al. (2007) reported a small morning-to-afternoon cortisol ratio in boys -but not girls- with attention problems, which suggests an atypical circadian rhythm. Also Sondeijker et al. (2007) reported ADHD problems to be associated with higher basal evening cortisol levels in a general child population sample. However, they reported the opposite effect of sex of child

compared to Susman et al. (2007) with high rates of ADHD problems being associated with higher awakening cortisol levels in boys, but not in girls. Studies considering only awakening values also suggested a dysregulation of the HPA axis in ADHD, although findings were inconsistent. Some authors found a lower cortisol awakening response in a group of children with ADHD compared to a group of controls (Blomqvist et al., 2007; Ma et al., 2011), whereas Hatzinger et al. (2007) found higher morning peak levels in a much younger population sample of boys with hyperactivity symptoms. In contrast to previous findings, two recent studies failed to find any difference on morning cortisol between children with ADHD (without comorbid disorders) and control children (Freitag et al., 2009; Wang et al., 2011). Only one study has examined this in adults which reported no effect of ADHD diagnosis (Hirvikoski et al., 2009): Both the overall cortisol levels and the typical diurnal cortisol rhythm, including the awakening response, were normal in ADHD.

Considering the high comorbidity rates of ODD in ADHD, inconsistent results may be explained by confounding effects of ODD. According to the hypo-arousal theory (Quay, 1965; Raine, 1996), disruptive disorders such as ODD and CD are linked to lower basal cortisol levels and lower stress responses (McBurnett et al., 2000; Moss et al., 1995; van Goozen et al., 2000; van Goozen et al., 1998), but also to lower morning values (Pajer et al., 2001; Shirtcliff et al., 2005). Results relating to ADHD with comorbid ODD/CD are inconsistent. Some authors confirmed a hypo-arousal pattern in children with ADHD+ODD measuring both awakening (Freitag et al., 2009) and basal values (Kariyawasam et al., 2002) while other authors failed to find any robust association between waking levels and comorbid problems in ADHD (Hastings et al., 2009). In line with these findings, no differences in basal levels between ADHD children with aggression and without aggression have been reported (Schulz et al., 1997), suggesting the possibility that certain characteristics of ADHD, rather than aggression, could be associated with cortisol levels. Very recently, this complex relation

between ADHD-ODD comorbidity and diurnal cortisol profiles has become a focus of interest. In the study of Imeraj et al. (2012), salivary cortisol was sampled five times a day (awakening, 30 min after awakening, noon, 4PM, 8PM). Their findings supported time-related arousal disruptions in children with ADHD associated with the presence or absence of ODD comorbidity. More specifically, it seemed that the ADHD subgroup without ODD comorbidity showed a flatter slope with relative morning hypo-arousal and evening hyperarousal, whereas the ADHD+ODD subgroup showed a steeper slope with relative morning hyperarousal and evening hypo-arousal.

2.2.4.3. Heart rate.

As arousal involves activation of the autonomic nervous system, physiological dysregulation of this system could be related to several psychiatric disorders involving arousal problems (Dietrich et al., 2007; Lorber, 2004; Ortiz and Raine, 2004). For example, a relation between low basal heart rate and disruptive behaviors has been established by several authors (Lorber, 2004; Mezzacappa et al., 1997; Ortiz and Raine, 2004). However, results on autonomic functioning in ADHD are less clear. Moreover, studies focusing on full circadian patterns are still limited despite the well-known time of day effects in heart rate. Recently, normal intrinsic circadian rhythms have been described (Waterhouse et al., 2007): an average day-night difference in resting heart rate of 6.5 bpm has been replicated by several authors (Burgess et al., 1997; Kerkhof et al., 1998; Scheer et al., 2003).

Research in relation to ADHD has mainly focused on specific laboratory conditions such as stress inducing performance (Lackschewitz et al., 2008), peer provocation (Waschbusch et al., 2002), performance (Borger and van der Meere, 2000; Crone et al., 2003), and reward (Beauchaine et al., 2001; Crone et al., 2003; Crowell et al., 2006; Iaboni et al., 1997; Luman et al., 2007). Pre-test heart rate usually did not differ between subjects with ADHD and normal controls (Iaboni et al., 1997; Lackschewitz et al., 2008). However, these

levels may be influenced by anticipatory stress and studies have tended not to investigate time of day fluctuations in ADHD. Only recently, a study on 24-hour heart rate patterns in ADHD has been completed (Imeraj et al., 2011).

Crowell et al. (2006) reported lower basal heart rate (pre-test value) in children with ADHD+ODD. Herpertz et al. (2001) compared ADHD groups with and without comorbid CD - they reported lower autonomic responses in the comorbid but not in the ADHD-only group, relative to controls. Although non-specific skin conductance responses were significantly different between groups in this study, this was not the case for resting heart rate levels. In contrast, van Lang et al. (2007) reported a higher mean basal heart rate (measured between 1 pm and 5 pm) in a group of children with high scores on ADHD+CD/ODD compared to a group with ADHD without comorbidity. These results suggest that differences in basal heart rate and autonomic functioning could be due to confounding effects of comorbidity, medication, and time of day.

Recently, Tonhajzerova et al. (2009) found that unmedicated children with ADHD without comorbid disorders were more likely to display tachycardia compared to normal controls during a short-term evaluation (3 intervals of 5 minutes) in both supine position and orthostasis. These measurements were conducted between 8 AM and noon. Although this study was limited by a small sample and possible confounding effects of stress in a laboratory setting, spectral analysis of these results indicated changes in the cardiac autonomic regulation, i.e., decreased cardiac vagal modulation in supine position and altered ability of dynamic activation of the autonomic nervous system in response to orthostasis. It has been hypothesized that such an autonomic imbalance -low parasympathetic activity and a relative sympathetic dominance- reflects low heart rate variability, a marker for prefrontal hypo-activity (Thayer and Sternberg, 2006) as seen in ADHD (Arnsten, 1998; Halperin and Schulz, 2006; Himelstein et al., 2000; Valera et al., 2007). Very recently, the finding of higher heart

rate levels in non-medicated children with ADHD was confirmed during a 5-day heart rate

registration study (Imeraj et al., 2011). Additional analyses revealed that group effects were

larger at specific times of the day, namely afternoon and nighttime hours; a finding

independent of activity and comorbid psychiatric disorders. The authors suggested that time

of day may be an important contributor to altered heart rate patterns in ADHD. Especially the

increase in nighttime levels, i.e., resting heart rate, seems important as this measure refers to a

lower vagal tone which is associated with cardiovascular disease and mortality (Thayer and

Lane, 2007).

2.2.5 Summary of findings, limitations and clinical implications of research to date.

Although patchy and inconsistent, this review found initial support for disrupted

circadian rhythms in ADHD with respect to each area reviewed. First, a circadian phase delay

was suggested in (at least a subgroup of) subjects with ADHD. This evidence was clearest in

relation to chronotypology and sleep-wake rhythms, pointing to an association of ADHD with

self-reported optimal arousal later in the day (i.e., *eveningness*) and with later sleep times,

difficulties with morning awakenings, and excessive daytime sleepiness earlier in the day.

The idea that the biological clock is responsible for this delayed timing of sleep-arousal states

in ADHD was further supported by melatonin studies showing a delayed DLMO in a

subgroup of subjects with ADHD and chronic SOI, which improved after melatonin treatment.

Second, on the behavioral level, studies supported time of day effects in attention,

performance, and activity. However, group differences were particularly expressed during

afternoon hours, which runs counter to the previously hypothesized circadian phase delay.

One possibility is that optimal arousal levels in children with ADHD are set at later times of

the day as compared to controls, but both still occur in the morning/noon rather than the

afternoon. Alternatively, more overt problematic behavior could be the result of a complex

interaction between specific times of day (especially afternoon) and contextual conditions (e.g., high cognitive, self-regulatory demands).

Finally, published data on across the day fluctuations in cortisol and heart rate, although inconsistent, provide some additional support for this point of view. With respect to cortisol, most data support differential diurnal cortisol patterns in ADHD, but the specific time points (awakening vs evening) responsible for this circadian effect could not been established. Very recently, the evaluation of diurnal cortisol patterns during multiple days revealed that ADHD with or without ODD subgroups may be hypo- versus hyperaroused at different times of the day (Imeraj et al., 2012). Despite well-established across the day fluctuations in heart rate in normal populations, in ADHD, this measure has mostly been examined in relation to stress without taking into account possible time of day effects. There is only one longer-term evaluation of heart rate in ADHD. In this study, children with ADHD showed higher heart rate levels which were particularly expressed during the night and the afternoon, suggesting that circadian effects are important in explaining autonomic dysfunction in ADHD (Imeraj et al., 2011).

These results must be interpreted in the light of study limitations. First, most of the studies were not designed to investigate time of day effects in ADHD and so the results may be confounded by factors that influence the endogenous biological clock function. Potential confounders include; (i) environmental factors such as light, climate and latitude; (ii) developmental factors such as age, sex, pubertal stage, menstrual cycle stage; (iii) factors related to health status (including tobacco use, caffeine intake, and alcohol consumption) and disease characteristics (including ADHD severity, subtype, comorbidity, and medication status); and (iv) factors as stress, digestion, motivation, and physical exercise (Atkinson et al., 2007; Blatter and Cajochen, 2007; Carskadon et al., 1993; Cortese et al., 2006; Portaluppi et al., 2008).

Second, studies have typically used a small number of measures evaluated during relative short observation periods. This limits the interpretability and generalizability of results across biological and psychological systems. In circadian research, combinations of measures have been suggested to be important as interactions and common pathways between several circadian markers have been described. For example, there is a mutual link between the autonomic nervous system and the HPA axis: sympathetic activation results in higher production of CRF and therefore, also of cortisol; inversely, corticotropin releasing factor (CRF) stimulates noradrenergic neurons (Chrousos and Gold, 1998; Sondeijker et al., 2007). Also interactions between melatonin and cardiovascular function (Scheer et al., 2003; Zawilska et al., 2009), between melatonin and body temperature (Zawilska et al., 2009) and between HPA axis functioning and sleep patterns have been reported (Buckley and Schatzberg, 2005; Edwards et al., 2001). High inter- and intra-day variability in these circadian measures warrants longer-term evaluations (Bartels et al., 2003; Edwards et al., 2001; Houtveen and de Geus, 2009; Schulz et al., 1997).

Finally, previous research does not assess which mechanisms may underpin the association of disrupted circadian rhythms and ADHD and does not allow inferences to be drawn about the causal role of such circadian effects. On the one hand, a delayed timing of sleep-arousal states by the SCN seems to be important in subjects with ADHD. Though this finding could probably not be generalized to all subjects, considering the heterogeneous nature of ADHD, a disrupted circadian regulation of arousal could aggravate ADHD symptoms or could even represent a specific developmental pathway in at least some cases. On the other hand, in general, arousal dysregulation in ADHD seems to be associated with a more complex pattern of behavioral problems throughout the day, which are even more expressed in interaction with environmental and stress-related events.

Despite inconsistencies in studies and methodological limitations the emerging evidence for circadian effects may eventually have practical value. For example, children with ADHD and comorbid insomnia (aged 6-14) were reported to benefit from exogenous melatonin administration -with or without combined stimulant medication treatment. It may therefore be valuable to routinely evaluate sleep problems in ADHD to detect this subgroup and improve their outcomes. Although light therapy seems effective in adults with ADHD and a delayed sleep phase (Rybak et al., 2004), so far, no melatonin medication studies in this population are available. Well-designed studies to establish optimal dosing regimens for different age groups and long-term safety are needed (Bendz and Scates, 2010).

Identifying the afternoon as a period of risk for ADHD (especially when there is an overlap with high environmental demands) may encourage further educational adaptations considering the timing of academic lessons. Relatedly, adjustment of dosing and timing of ADHD medication to optimally observe and treat problematic behavior considering its fluctuating expression should be considered. Systematic methods of assessment of time of day effects for clinical purposes need to be developed (Chavez et al., 2009; Pelham et al., 2001; Sonuga-Barke et al., 2004; Swanson et al., 2004). Though the specific mechanisms that may underpin time of day effects in arousal dysregulation are still unknown, such knowledge may guide specific therapeutic choices for individual patients as arousal levels are often the target of focus for interventions. For example, according to Stadler et al. (2008), children with a lower basal heart rate, i.e., lower autonomic arousal, profit less from psychotherapy than children with higher basal heart rate. In contrast, stimulant medication increases arousal, and it may therefore be especially useful at times of underarousal (Hermens et al., 2007; but see section 3.3 for more detailed information on action mechanisms). Such adaptations in the timing of arousal-based treatments may be particularly relevant in different ADHD subgroups (e.g., with or without ODD). As nighttime tachycardia has been reported in unmedicated

children with ADHD, this might question the use of stimulant medication that could further

increase heart rate levels (Daniels, 2009; Hammerness et al., 2011). Though Vitiello et al.

(2012) concluded that stimulant treatment in ADHD probably does not increase the risk for

hypertension over a 10-year period, the persistent adrenergic effect on heart rate during

treatment may be an important issue especially for adult's with ADHD who are at risk due to

higher rates of adult obesity and tobacco use (Cohen et al., 1999; Young and Bray, 2007). As

in normal populations, an association of circadian misalignment with obesity and other

cardiovascular risk factors has been reported, this could even further increase health risks in

ADHD (Gangwisch, 2009; Scheer et al., 2009).

3. LC-mediated Arousal Dysfunction in ADHD – A Working Hypothesis

Linking Context-driven, Cognitive Energetic, and

Context-independent Circadian-based Alterations.

Studies to date provide a fragmented pattern of circumstantial evidence linking ADHD

to altered circadian rhythms. A more systematic approach to studying the relationship

between time of day effects and ADHD needs to be established and this in turn needs to be

built on a platform underpinned by biologically and psychologically plausible models. Here

we describe one such framework established on a working hypothesis of the biological basis

of putative circadian disruptions in ADHD, their links to other aspects of ADHD function,

and their biological and psychological roots. In this hypothesis we postulate that circadian

disruptions are one aspect of a more general arousal regulation problem that has already been

identified as the basis for a range of cognitive-energetic deficits in ADHD (Sergeant and Van

der Meere, 1988, 1990). More specifically, we suggest an extension of models of altered

arousal mechanisms in ADHD (Sergeant and Van der Meere, 1988, 1990) encompassing both

cognitive energetic effects due to altered responses to changes in environmental context and

disrupted patterns of spontaneous circadian activity across the day. Therefore in addition to

the pattern of findings relating to circadian effects in ADHD reported above this model is

built on two areas of well established existing evidence. First, that LC function, as a key locus

in noradrenergic pathways in the brain is implicated in arousal more generally and circadian

effects specifically. Second, the evidence that arousal mechanisms are altered in ADHD

leading to general difficulties in regulating physiological state in response to changing

conditions. These patterns of evidence highlight the potential role of the LC disruption in

ADHD as a biological mediator of both context specific cognitive energetic effects and

context independent circadian effects (This model is represented in figure 1). In the following

section, we review the literature linking LC function (and noradrenergic function more

generally) to (i) arousal and circadian processes and (ii) ADHD pathophysiology more

generally. We then identify areas for future research exploring the role of LC dysfunction

specifically in relation to circadian effects in ADHD (see section 4).

3.1. The Role of Locus Coeruleus in Arousal and Circadian Effects

The LC, the main noradrenergic nucleus in the brain, is responsible for the regulation

of cortical arousal which can be described as a physiological and psychological state of being

awake, aware and alert (Aston-Jones, 2005; Samuels and Szabadi, 2008). Arousal involves

the activation of the reticular activation system (RAS) in the brain stem, the autonomic

nervous system and – if induced or accompanied by stress- the endocrine system (Pfaff and

Banavar, 2007; Pfaff et al., 2007; Schwartz and Roth, 2008; Silver and LeSauter, 2008). Next

to arousal-influencing effects of factors such as hormonal stress reactivity, emotions,

temperament, and psychopharmacotherapy, it is assumed that arousal state regulation is also

driven by circadian rhythms (Silver and LeSauter, 2008). A correct timing of the circadian

clock (SCN) is important to orchestrate neural activity, regulate sleep-wake states, and control

emotion and cognition functions (Vicentic et al., 2009).

The hypothesis that the LC shows fluctuations in diurnal activity has been supported in animals. Aston-Jones (2005) described an indirect projection from the SCN, the circadian pacemaker, to the LC with the dorsomedial hypothalamic nucleus (DMH) as a relay from the SCN to the LC. The DMH plays a major role in circadian rhythms of corticosteroid and other endocrine secretion, locomotor activity, and sleep (Chou et al., 2003; Germain and Kupfer, 2008). In this SCN-DMH-LC circuit, wakefulness is induced by hypocretin/orexin neuropeptides activating the arousal-related LC (Ivanov and Aston-Jones, 2000), and inversely, suppressing the sleep-related ventrolateral preoptic areas (VLPO) (Winsky-Sommerer et al., 2003).

When noradrenaline (NE) is released from the LC, it exerts unique and additive wake-promoting actions through binding on noradrenergic receptor subtypes α_1 and β (please see Berridge and Waterhouse (2003) for a more detailed review). Such noradrenergic release in the cortex may produce a prolonged depolarization of cortical neurons that would increase their responsiveness to other inputs, for example dopaminergic prefrontal cortex (PFC) circuits (Gorelova et al., 2002). In contrast to α_1 and β receptors that are thought to exist at postsynaptic sites primarily, α_2 receptors can be found both pre- and postsynaptically. Binding of NE on the α_2 receptor has sedative effects. Pre-synaptic receptors provide a local feedback mechanism for counteracting excessive release of NE (please see Berridge and Waterhouse (2003) for a more detailed review). Though clonidine, an α_2 noradrenergic agonist, decreases LC firing (thus suppresses NE release), it enhances cognitive performance through binding on postsynaptic receptors in PFC (Berridge and Devilbiss, 2011). This way, the LC-NE system has been reported to be involved not only in (i) initiation of behavioral and neuronal activity ready to collect sensory information (e.g., waking), but also in (ii) modulation of sensory information processing, attention, and memory within the waking state (Berridge and Waterhouse, 2003). These behavioral processes have been associated with

different discharge modes of LC: The tonic noradrenergic release (i.e., spontaneous, baseline activity of the nucleus; which shows a circadian rhythm with an increase from sleep to waking) and the phasic discharge (i.e., brief, rapid increases in response to environmental stimuli when awake). In the latter case, phasic activation takes place in response to the processing of task-relevant stimuli and optimalizes task performance (only possible when tonic discharge levels are moderately increased), whereas in the tonic mode (high levels of ongoing tonic activity), the LC fails to respond phasically to task demands an effect associated with poor focused attention and exploration (Aston-Jones and Cohen, 2005). Parallel to the Yerkes-Dodson relationship between arousal and performance, the authors proposed a theory stating that optimal performance is associated with moderate LC tonic activity and prominent phasic LC activation and that poor performance is associated with both low levels (inattentive, drowsy, sleepy) and high levels (distractible) of tonic activity, with small or even absent LC phasic responses. As the LC is associated with both circadian regulation and cognitive performance, Aston-Jones and colleagues (2001) hypothesized that circadian changes in LC activity may be reflected in complex task behavior, such as a circadian fluctuation in cognitive ability, next to alterations in sleep-wake cycles.

3.2. ADHD, Arousal and Deficient State Regulation

In ADHD the best evidence of arousal-related dysregulation comes from studies of the impact of changing environmental context on information processes. These have usually been interpreted in the light of state regulation deficits using cognitive energetic models (Sergeant and Van der Meere, 1988, 1990). Sergeant and Van der Meere (1988, 1990) first interpreted the non-optimal state of arousal as due to failures to appropriately allocate effort during information processing. In this model state dysregulation refers to an imbalance between three, closely linked, energetic systems, namely effort, arousal and activation. Difficulties in state

regulation in ADHD are predicted to arise not only from under arousal/activation but also due to over arousal/activation (Sonuga-Barke et al., 2010; Van der Meere, 2005).

To date, taken from this perspective, the focus of the primary deficit in ADHD relates to the response preparation-related activation processes which are associated with response organization. In their review, Sonuga-Barke et al. (2010) point to investigation of cognitive performance in ADHD children during tasks with different event rates (the key probe of activation processes) which provide support for environmental influences on state-regulation, the importance of 'optimal' stimulation and relevance of the inverted U-curve (parallel to the Yerkes-Dodson relationship) linking event rate to performance via arousal/activation levels: during fast event rate, ADHD children responded fast and inaccurate, while during slow event rate, they are expected to show slow-inaccurate responding. Although there is currently little research on the neurobiological correlates of this deficit, a role for LC dysfunction has been suggested (Sonuga-Barke et al., 2010). This suggestion shifts the primary focus of interest from dopaminergic to noradrenergic deficits in ADHD. For a long time, the dopamine theory (Levy, 1991) has been the leading dogma, suggesting an inhibitory dopaminergic effect at prefrontal/striatal level in ADHD, which has repeatedly been supported by neuroimaging, genetic and stimulant medication studies (Faraone and Biederman, 1998; Faraone and Khan, 2005; Levy and Swanson, 2001; Solanto, 1984). More recent data, however, suggest an important modulating role of the LC and noradrenergic arousal pathways on dopaminergic PFC function.

3.3 Existing Evidence Implicating LC-related Noradrenergic Function in ADHD

The cognitive-energetic models described above hypothesize that state regulation deficits are in part related to LC dysfunction (Sergeant and Van der Meere, 1988, 1990). Tonic activity of the LC system, located in the RAS, is associated with the regulation of arousal and several state-dependent processes, such as sensory information processing,

attention, working memory, and motor processes (Arnsten and Dudley, 2005; Devilbiss and Waterhouse, 2004; Sonuga-Barke et al., 2010). Below we hypothesize that the pathophysiology of ADHD involves an 'overdrive' of the LC, with excessive noradrenergic tonic release leading to reduced capacity of the PFC to respond to phasic stimuli (Mefford and Potter, 1989; Pliszka et al., 1996; Sonuga-Barke et al., 2010). More specifically, the increase in tonic discharge above a certain level has been associated with less robust phasic discharge and decrease in focused attention and increase in impulsivity (Aston-Jones and Cohen, 2005). Reciprocal connections between the PFC and the LC have been hypothesized by Arnsten et al. (1996), pointing to the role of noradrenergic in concert with dopaminergic systems in explaining prefrontal dysregulation (Levy and Swanson, 2001). Studies showed that NE may enhance "signal/noise" processing in the PFC via actions at α_2 receptors (increase signal) and impair its function via α_1 and β receptors; these processes coincide with optimal dopamine (D_1) stimulation (decrease noise) and excessive D_1 stimulation respectively (see review Arnsten, 2006). Therefore, the authors suggest that catecholamines may act as a chemical switch: turning on PFC during normal waking and turning it off during drowsiness or stress.

With respect to ADHD, monkey models with blockade of the α_2 receptors of the PFC created symptoms of ADHD (hyperactivity, impulsivity, and impaired working memory), whereas clonidine, an α_2 noradrenergic agonist used in the treatment of ADHD, has cognitive-enhancing effects due to its ability to activate post-synaptic α_2 receptors (see review Berridge and Devilbiss, 2011). Other treatment modalities in ADHD support (modulatory) deficits in noradrenergic pathways (see Berridge and Devilbiss, 2011; Biederman and Spencer, 1999; del Campo et al., 2011 for reviews on this topic). For example, beneficial arousal-promoting effects of psychostimulants are due not only to extracellular increases in dopamine but also in NE concentrations in the PFC (Devilbiss and Berridge, 2008). Looking more closely at electrotonic coupling, on the level of the LC, low-dose administrated stimulants moderately

decreased the tonic discharge (which is however overcompensated by drug-induced elevations in extracellular NE), but largely preserved phasic signaling which is important in the regulation of behavioral actions (Berridge and Devilbiss, 2011). Also modafinil, an analeptic drug used in the treatment of narcolepsy and excessive daytime sleepiness, has been suggested to shift the LC to low tonic, high phasic activity which potentially enhances PFC function in ADHD (del Campo et al., 2011). Additionally, tricyclic antidepressants (noradrenergic reuptake inhibitors) have been described to be effective in the treatment of ADHD symptoms through an increase of extracellular NE in the PFC by blocking noradrenergic reuptake (Biederman and Spencer, 1999). Finally, the idea that modulation of noradrenergic circuits may improve ADHD symptoms is supported by the newer ADHD agent atomoxetine, which is also a selective inhibitor of noradrenergic transporters. Swanson et al. (2006) showed that atomoxetine increases NE in several brain regions including the PFC and dopamine in the PFC (not in other regions such as striatum and nucleus accumbens). Therefore, atomoxetine is assumed to have less abuse potential as compared to methylphenidate. The clinical use of atomoxetine has moreover been promoted in terms of its 24-hour treatment of inattention, hyperactivity/impulsivity. Though it needs to be further investigated to what extent this drug modulates circadian rhythm in humans with ADHD, recent data suggest that atomoxetine may reset the circadian clock in mice (O'Keeffe and al., 2012). Finally, atomoxetine is considered to be a first-line treatment in patients with comorbid anxiety or tics (Garnock-Jones and Keating, 2009).

3.4. A Working Hypothesis: Circadian Effects as a Special Case of LC / Arousal Dysfunction in ADHD

Based on the above review we postulate that in this case state regulation problems and altered circadian effects in ADHD both arise from shared origins in dysfunctional SCN-DMH-LC pathways (see Figure 1). This hypothesis is based specifically on the idea that (i)

ADHD is associated with tonic hyperactivity of the LC (as described above in the state

regulation model; Mefford and Potter, 1989; Pliszka et al., 1996; Sonuga-Barke et al., 2010),

and (ii) that the LC itself is integrally involved in the regulation of circadian effects generated

by the SCN (Aston-Jones et al., 2007), next to its role in behavioral states and cognitive

performance.

Direct evidence for the functionality of the SCN-DMH-LC circuit comes from patients

with a lesioned SCN who fail to modulate attention, dysregulating the timing of the attention

focus (Cohen et al., 1997). Also with respect to hyperactivity, Sylvester et al. (2002)

described a modulating role of SCN as suggested in studies with rats (Stephan and Zucker,

1972). Though little techniques are available yet to detect dysfunctions of the SCN (Sylvester

et al., 2002), clock gene polymorphisms are expected to alter the timing of the circadian

pacemaker (Rosenwasser, 2010). With respect to ADHD, Levitan et al. (2004) suggested a

link between polymorphisms of the 7-repeat allele of the dopamine receptor D_4 gene (DRD-4),

ADHD and circadian rhythm problems. Other authors have recently established a more direct

link between ADHD and genetic circadian dysregulation by describing a significant

association between polymorphisms of the 3'-untranslated region of the CLOCK gene -a gene

previously linked to both sleep disturbances and evening preference- and ADHD (Kissling et

al., 2008; Xu et al., 2010). Also Brookes et al. (2006) detected associations between two

genes in the circadian rhythm system and ADHD. Very recently, Yan et al. (2011) pointed to

additional evidence linking disruption in circadian rhythms with ADHD. In their NK1

receptor lacking mice, resembling abnormalities in ADHD, performance varied as a function

of time of day and for some measures of response control an interaction between NK1

function and circadian rhythms was observed. The authors mention that this is not surprising

as NK1R are prevalent in regions responsible for circadian control (e.g., SCN) and antagonist

agents have been reported to cause daytime fatigue, insomnia, and disruptions of circadian

motor activity. On the level of DMH, lesions have also been reported to reduce circadian rhythms of wakefulness, locomotor activity, and cortisol levels (Chou et al., 2003). On the level of the LC, there is evidence for a circadian rhythm in its impulse activity and its role in producing transitions between sleep-waking cycles; after lesions of the LC, a decrease in the amplitude of the circadian rhythms in sleep-wake cycles was noted as described in reviewed work of Aston-Jones and colleagues (Aston-Jones et al., 2007). In their experiments, they additionally showed that light deprivation caused substantial decreases in noradrenergic neurotransmission in the rat's frontal cortex.

Despite the role of the LC in circadian regulation, it is currently not known whether an overdrive of this nucleus is specifically associated with a circadian phase delay. However, this hypothesis is highly plausible; Aston-Jones and colleagues hypothesized that upregulated noradrenergic release may contribute to both sleep (e.g., sleep onset insomnia) and behavioral symptomatology (e.g., daytime hyperactivity and inattention) in ADHD, as they observed these specific ADHD types of behavior during the tonic mode of activity in monkey LC. Though we assume that sleep onset problems may subsequently lead to difficulties with awakening and daytime sleepiness, these problems may also relate more directly to hyperactive tonic discharge of the LC. With respect to morning awakening, an increase in tonic activity is needed for transition from sleep to wake. High baseline levels are however associated with less variability (Phillips et al., 2000) (see section 4.1.b; pupil diameter), which may hypothetically impede such transitions. During wake, changes in the tonic and subsequently phasic activity of the LC have been associated with fluctuations in alertness under specific conditions (Aston-Jones, 2005). As in our review above it was noted that ADHD behavior becomes more overt at specific times of day, it is reasonable to hypothesize that the two functions of the LC - its role in both state control and performance- interact and that 'baseline LC hyperarousal' in ADHD leads to a complex profile of circadian-regulated

and context-dependent behavioral dysregulation. It still needs to be determined though how time of day effects would interact with the expression of the tonic/phasic mode of LC activity –or transitions between them- to affect prefrontal functioning.

INSERT FIGURE 1 ABOUT HERE

Though highlighting the link between circadian alterations and ADHD may allow us to identify novel processes for study in ADHD, the complexity of the working hypothesis presented above must be recognized (see Figure 1). First, neurotransmitter systems do not operate independently, and the interaction between NE, dopamine, and serotonin is probably important in psychopathology (Harvey et al., 2011). In addition to the noradrenergic circuitry described above, dopaminergic and serotonergic dysfunctions may additionally link circadian alterations to ADHD as these neurotransmitters are themselves influenced by the circadian rhythm system and considered to be pathophysiologically involved in ADHD (Faraone and Khan, 2005; Levy, 2009; Paclt et al., 2005; Pattij and Vanderschuren, 2008; van der Kooij and Glennon, 2007). Second, complex interactions between neurotransmitters, clock genes, and circadian neurobiological structures have been described. For example, Barnard and Nolan (2008) refer to the fact that clock gene expression is modulated by neurotransmitter effects. The circadian clock has also been described to be influenced by an 'overdrive' of the LC and related increase in noradrenergic activity (Maurizi, 1984) such as seen in ADHD. This could be due to inadequate noradrenergic stimulation of the pineal gland, altering the concentrations of its main hormonal product melatonin, which in turn is important in the regulation of the circadian clock containing melatonin receptors (Pacchierotti et al., 2001). Finally, the idea that circadian alterations are an expression of ADHD-related arousal-based problems is probably only valid for a specific subsample of subjects with ADHD, and may also be present in other psychiatric disorders. This hypothesis is in line with for example

findings that executive functioning deficits and delay aversion are implicated in ADHD, though that neither is necessary for ADHD nor specific too it (Sonuga-Barke et al., 2008).

4. Proposals for Future Study of Circadian Effects in ADHD

In this section we discuss future directions for research indicated by the LC-based model of circadian effects described above and described in Figure 1. Multilevel interdisciplinary research will be necessary to address the current gaps in this research area. At this point, there is evidence for a link between ADHD, dysregulated arousal and LC, and a link between LC and circadian rhythms (described above). More systematic research however is needed to investigate circadian-related effects in ADHD to confirm currently available findings presented in the review.

Based on the model proposed above, we formulate the following predictions: (i) *ADHD is associated with LC-mediated circadian rhythm alterations*; subpredictions are: (a) LC tonic hyperactivity in ADHD is more expressed at specific times of day than others; (b) there is a disruption in the circadian rhythms of LC-noradrenergic mediated arousal in ADHD; (c) subjects with ADHD show specific alterations in behavioral and physiological measures as a function of time of day; (d) circadian disruptions in LC activity, arousal, and behavioral/ physiological measures will be correlated in ADHD; (ii) *there is an interaction of time of day effects and specific environmental stimuli* suggesting a 'shared LC state-regulation pathway deficit' in ADHD; and (iii) the theory of disrupted circadian rhythms is probably *only valid for a subgroup of cases with ADHD* and may overlap with other psychiatric conditions.

4.1. Prediction 1: ADHD is Associated with LC-mediated Circadian Rhythm Alterations

a. LC tonic hyperactivity in ADHD is more expressed at specific times of day than others.

ADHD has been associated with an 'overdrive' of the LC (Mefford and Potter, 1989; Pliszka et al., 1996; Sonuga-Barke et al., 2010), which is in turn involved in the circadian

regulation of arousal and sleep-wake states (Aston-Jones et al., 2007). These findings rely heavily on animal studies, but it is reasonable –though still challenging- to investigate the LC in humans with ADHD and to detect whether the LC dysfunction in ADHD is circadian sensitive. One way to do so is the use of neuroimaging methods, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). To address this question imaging procedures need to be repeated across a 24-hour period. During daytime hours, this has been done before not only for visualization of circadian activity in the LC but also in the SCN (Schmidt et al., 2009), when subjects were exposed to different environmental stimulus/task conditions at different times of day. Scanning during sleep will be cumbersome but is theoretically feasible. However, practical problems may arise as it is difficult to fall asleep during scanning procedures. A PET protocol to study sleep in a naturalistic setting has been provided, though with decreased temporal resolution (Nofzinger et al., 1998). In this regard, less invasive, peripheral arousal measures and electroencephalogram (EEG) (as described in the second and third subprediction) may be interesting to (additionally) study sleep in humans.

Pharmacological studies also allow investigation of the LC function and activity. For example, studies with clonidine used for ADHD or as an anesthetic have provided in-depth knowledge on sleep-wake and cognition regulatory functions through the study of binding on pre- and postsynaptic α_2 adrenergic receptors (see for reviews: Arnsten et al., 1996; Berridge and Devilbiss, 2011). Another example relates to disruption of circadian rhythms in dopaminergic concentration and receptor activity which have been linked to circadian symptomatology in drug addiction (Falcon and McClung, 2009; Naber et al., 1980; Sleipness et al., 2007). In their review, Manev and Uz (2009) reported time-dependent behavioral actions of both cocaine and amphetamines. In relation to noradrenergic receptors, circadian rhythms are thought to be modified by tricyclic antidepressants (Wirz-Justice et al., 1980). It

will be valuable to explore time-dependent effects on ADHD drugs' working mechanisms considering both dopaminergic and noradrenergic pathways. Such knowledge could guide more systematic effect-evaluation studies taking into account time of day effects of different drug-releasing modalities for ADHD (Swanson et al., 2004) to treat time-specific arousal problems in this population (see prediction 2).

b. There is a disruption in the circadian rhythms of LC-noradrenergic mediated arousal in ADHD.

In recent research, the utility of two candidate psychophysiological markers of LC-noradrenergic activity has been investigated: the P3- event related potential (ERP) and pupil diameter (Murphy et al., 2011). The P3 is an ERP component peaking 300-600 ms after a task-relevant stimulus, which has been argued to represent a cortical electrophysiological correlate of the phasic LC response and the noradrenergic potentiation of information processing (Nieuwenhuis et al., 2005). A second index is pupil diameter, an autonomic measure involving both sympathetic and parasympathetic activity, which has been hypothesized to reflect both tonic and phasic aspects of LC activity. More specifically, upregulation of tonic noradrenergic activity has been associated with increases in baseline pupil diameter and decrease in pupillary variability, while pupil dilatory response occurs to a wide range of task-related stimuli (Phillips et al., 2000).

To confirm the circadian-related prediction above, it would be necessary to assess baseline pupil diameter at different times of the day in both cases with and without ADHD. Because of the close relation between tonic and phasic activity in daytime cognitive performance it is important to detect whether ADHD-associated increases in tonic activity (and therefore larger pupil diameter baseline) are more expressed at different times of the day. With respect to the P3, which is assumed to reflect phasic activity, amplitudes have often been found to be smaller in ADHD as compared to controls (Barry et al., 2003b). There is evidence

that P3 differences in ADHD are related to arousal states: for example, in their event rate

study, Wiersema et al. (2006a; 2006b) found altered P3 components in the ADHD as

compared to a control group only when in underaroused state. However, as of yet, no study

has evaluated time of day effect on P3 deviation in ADHD. Suggestions to investigate the

circadian-environmental overlap are discussed in prediction 2.

Though pupillometry is often used in research on daytime sleepiness (decreased pupil

size due to parasympathetic influence) under both light and darkness conditions,

measurements can not be made "during" sleep. With respect to P3, small or even absent

potentials are expected during sleep as low tonic firing rate does not allow phasic discharge.

Though studies analyzing auditory input during sleep observed a sleep P3, it is uncertain to

what extent this potential is equivalent to waking P3 (Bastuji et al., 2002). Nevertheless,

further investigation of the role of the LC in regulating autonomic nervous system and sleep-

wake cycles is important as fluctuations in a variety of measures of "arousal state" (e.g., heart

rate) have been reported to affect P3 morphology (Polich and Kok, 1995). Such peripheral

measures may provide an excellent alternative to monitor arousal states during both night and

day (see also description in prediction 1c): Nieuwenhuis et al. (2011) described in their review

that changes in LC activity are not only highly correlated with changes in P3 component and

pupil diameter, but also in skin conductance level and heart rate.

Alternatively, EEG is very suitable for this purpose as it is a direct index of the

electrical activity of the brain. More specifically, the θ/β ratio and α power in the EEG signal

have been used as a marker of central nervous system arousal. In ADHD, higher θ/β and α

deviances have been argued as an indication of cortical underarousal (see Barry et al. (2003a)

for a review). As of yet, there are no studies that evaluated time of day effects for these EEG

deviances. MSTL represents another option for the evaluation of daytime sleepiness and PSG

for more micro-evaluation of wake-sleep transitions and nighttime awakenings.

c. Subjects with ADHD show specific alterations in behavioral and peripheral

physiological measures of arousal as a function of time of day.

Though behavioral and physiological measures of arousal have value in the evaluation

of 24-hour patterns, studies evaluating these effects in ADHD have mostly been confounded

so far. Suggestions to address the issue of sample heterogeneity are discussed in prediction 3.

To control for environmental confounding effects, laboratory protocols have been developed

for circadian evaluations. The *constant routine protocol* controls for possible exogenous

factors in order to avoid their masking influences on the endogenous rhythm of the measured

variables. In this protocol, both contextual factors, such as light, feeding and activity, and

circadian measurement conditions are strictly regulated (Atkinson et al., 2007; Bailey and

Heitkemper, 2001; Blatter and Cajochen, 2007; Scheer et al., 2003). However, this

methodology not only raises financial, practical and ethical issues, especially in children, but

also the ecological validity of such procedure is questionable. Therefore, longer-term

evaluations in naturalistic settings, including multiple 'combined' measurements across

several days, are required (Houtveen and de Geus, 2009). As an extension to previous

research, we propose a longer term 'combined' approach that may include the assessment of

environmental information (e.g., lights out, daily activities), subjective and objective

sleep/wake assessments during several days and nights (e.g., actigraphy, DLMO, MSLT,

PSG), in addition to a 'full' circadian cortisol investigation (several measurements a day), 24-

hour registration of heart rate (with simultaneous 'control' measurement of activity), and

alternative measures which so far have not been carried out in ADHD. Useful alternative

measures could be for example blood pressure (Houtveen and de Geus, 2009), skin

conductance (Hot et al., 1999) and body temperature (Bailey and Heitkemper, 2001; Hofstra

and de Weerd, 2008). It must be noted however that some measures, for example of body

temperature, are probably not feasible in children as it is a relatively invasive procedure.

Finally, heart rate variability and spectral analysis of this measure are today one of the best methods to follow the activity of autonomic nervous system and its differential influences of the ortho- and parasympathetic branches during night.

   d. Circadian disruptions in different arousal-related measures (LC, arousal, and behavioral/ physiological measures) will be highly correlated in ADHD.

   Based on our working hypothesis, we expect that circadian effects on different arousal-related measures will be highly correlated within participants with ADHD. However, if circadian discrepancies between measures exist, this may reveal subtle differences in underlying neural processes. For example, when studying the circadian SCN-DMH-LC circuit, DMH lesions appear to eliminate circadian rhythms of corticosteroids but not melatonin (Chou et al., 2003). These authors hypothesize that a 'combined' disruption of cortisol and melatonin rhythm may be originated in the SCN –which is highly sensitive to melatonin input- rather than the DMH as other studies lesioning DMH and regions outside the DMH found circadian alterations in both measures.

   Examination of the correlation between peripheral and more fundamental measures is also warranted. Schmidt et al. (2009) studied the influence of circadian and homeostatic processes on cognitive performance in different chronotypes (morning vs evening) by imaging the LC and SCN (fMRI) during performance-related tasks (reaction times) at two test sessions (morning vs evening). Participants were also monitored by PSG at their preferred bedtimes during two consecutive nights; combined with assessments of subjective sleepiness, objective vigilance, and hourly collected saliva samples for assessment of melatonin phase starting 7 hours prior to habitual sleep time. Such a protocol might be adapted (oddball performance tasks) and extended with, for example, P3 ERP evaluation or pupil diameter response as these measures have been associated with information processing, reflecting phasic activity of the LC-noradrenergic system (Nieuwenhuis et al., 2005).

In our literature review some studies suggested a circadian phase delay in ADHD. Normally, during sleep and drowsiness there is low tonic activity, whereas tonic activity is increased when one is alert (Aston-Jones and Cohen, 2005). If a circadian delay is truly present in ADHD, following this reasoning this would mean relatively low tonic LC activity in the morning and relatively high tonic LC activity in evening. These deviations would both lead to non optimal performance: in the morning reflected by inattentive, drowsiness and being non-alert, in the evening by distractibility (see model Aston-Jones, page 406 in Aston-Jones & Cohen, 2005). At this point, it is difficult to say what phasic indices of LC will do, as during both (too) low and high tonic LC activity, phasic responses will be diminished (as can be measured by P3 component, pupil diameter response). In terms of baseline tonic LC activity, a smaller pupil diameter in the morning, but larger in the evening would be predicted.

4.2. Prediction 2: There is an Interaction of Time of Day Effects and Specific Environmental Stimuli Suggesting a 'Shared LC State-regulation Pathway Deficit' in ADHD

From a more theoretical perspective, current task protocols could be used at different times of the day to investigate the influence of arousing environmental stimuli on state regulation deficits in ADHD to see whether these results fluctuate across the day. In his study with NK1R-lacking mice, Yan et al. (2011) explicitly included the time of day during which mice were trained and tested. Based on their findings, the authors suggested that *"time of day might be a key variable in studies of ADHD patients and that the effect of an interaction between NK1R function and circadian rhythms on response control merits further investigation."* A concrete test of the interaction of time of day and environmental effects of arousal could be performed using event rate effects during different times of day, for example morning versus afternoon. Therefore, we additionally recommend longer-term evaluations of

ADHD behavior (both quantitative and qualitative) in different contexts or under different environmental conditions.

One context of interest would refer to the lab school protocol that is used in medication effect evaluation studies so far. This quasi-experimental naturalistic setting allows for the combined registration of behavior and additional measures (e.g., heart rate, saliva sampling) under different context conditions (e.g., academic tasks, free play) controlling for possible time of day effects. Though such protocols typically include ADHD children during summer camps, comparison with typically developing children would be interesting to detect during which specific situations and times of day group differences become more overt. This information would be very useful in the further evaluation of medication effects to treat problematic behavior especially at times when it is more expressed (Chavez et al., 2009; Pelham et al., 2001; Sonuga-Barke et al., 2004; Swanson et al., 2004).

Another context of relevance is stress. Though arousal is closely related to stress, Pfaff et al. (2007) provided a framework to understand the asymmetric relation between stress and arousal mechanisms, suggesting that stimuli causing stress are theorized to cause arousal, but inversely, that not all stimuli causing arousal are stressful. Whereas autonomic responses (e.g., heart rate) are activated in both stressful and non-stressful arousal conditions, the HPA axis (e.g., cortisol) is only activated in stressful conditions. Therefore, the combined diurnal assessment of heart rate and cortisol in diurnal evaluations could further explore to what extent underlying hypotheses relating time of day effects in arousal are specific for ADHD or whether they are the product of a more general stress-related dysregulation.

4.3. Prediction 3: The Association with Circadian Rhythm is Only Valid for a Subgroup of ADHD and May Overlap with Other Psychiatric Conditions

Considering the heterogeneous nature of ADHD, it seems necessary to determine whether alterations in peripheral measures and underlying pathways, if confirmed in ADHD,

are specific for some cases with the disorder or to what extent sleep-wake disruptions reflect a transdiagnostic phenomenon relevant across psychiatric disorders. Therefore, we suggest that future research should account for confounding effects related to age and sex characteristics, but also to ADHD subtype, ADHD severity, comorbidity with externalizing disorders (ODD, CD), internalizing disorders (anxiety, depression), or sleep disorders, and use of (stimulant) medication. One could aim to study homogeneous clinical samples, but -what may be even more fascinating- would be the use of a large-scale heterogeneous sample and a search for specific subgroups of patients with circadian dysregulation. Cases with ADHD and sleep-wake problems and cases with executive function (state regulation) deficit problems would be especially interesting to study. ADHD subgroups may be differentially affected by time of day effects; however, some may show *eveningness* chronotypology to inattention problems (Caci et al., 2009), whereas others reported the combined group to be more vulnerable for circadian problems (Chiang et al., 2010).

5. Conclusion

In line with evidence in other psychiatric disorders, the current literature provides some initial evidence of at least a subgroup of children with ADHD with circadian problems. Considering the heterogeneous nature of the disorder, it is plausible that anomalies related to one or more circadian measures reflect a distinct subgroup. Though it is not clear to what extent these problems are specific for ADHD at this stage, available evidence suggests that the circadian rhythm disruptions can at least modify severity and outcome, and may in some cases play a more etiological role. Although pathophysiological theories on ADHD so far largely ignored circadian effects on arousal and ADHD symptomatology, developing knowledge in several circadian domains, including underlying neurobiological mechanisms, led us to propose a working hypothesis that could serve as a framework for further research. In this putative model ADHD-related disruption of circadian processes and context-specific

effects on arousal-related processes such as cognitive energetic deficits are hypothesized to be

the result of LC dysfunction. Here we review the potential implications of this model for

clinical practice and future research.

Acknowledgements

Financial disclosures

Lindita Imeraj: no disclosures or conflicts of interest to report

Edmund Sonuga-Barke:

      Recent speaker board: Shire, UCB Pharma

      Current & recent consultancy: UCB Pharma, Shire

      Current & recent research support: Janssen Cilag, Shire, Qbtech, Flynn Pharma

      Advisory Board: Shire, Flynn Pharma, UCB Pharma, Astra Zeneca

      Conference support: Shire

Inge Antrop: no disclosures or conflicts of interest to report

Herbert Roeyers:

      Concultancy: Shire

      Research support: Shire, Lilly

      Conference support: Lilly

Roeljan Wiersema: no disclosures or conflicts of interest to report

Sarah Bal: no disclosures or conflicts of interest to report

Dirk Deboutte: no disclosures or conflicts of interest to report

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