Variability in Behaviour and Arousal Modulation
in Children with Attention-Deficit Hyperactivity Disorder:
Impact of Environmental Factors and
Circadian Characteristics

Lindita Imeraj

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Lindita Imeraj

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Promotor

Cornelis van Heeringen, MD, PhD (Ghent University)

Co-Promotor

Herbert Roeyers, PhD (Ghent University)

Support Committee

Dirk Deboutte, MD, PhD (Antwerp University)

Rudy Van Coster, MD, PhD (Ghent University)

Inge Antrop, PhD (Ghent University)

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Content

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a high impact child psychiatric disorder that affects 3-5 % of school-age children (Spencer, Biederman, & Mick, 2007; American Psychiatry Association, APA, 2000). This developmental disorder is defined by the presence of persistent and pervasive inattention, hyperactivity and impulsivity symptoms, which significantly impair daily functioning in the major life domains of the child, e.g., home and school (APA, 2000). Its onset is in early childhood (by definition before the age of 7), but in a majority of cases, ADHD symptoms persist into adolescent and adult life (for a review see: Spencer et al., 2007). Comorbid disorders during the lifespan are common in ADHD: for example, oppositional defiant disorder (ODD) and/or conduct disorder (CD) (30-60%), mood disorders (16-26%), anxiety disorders (10-15%), and learning disabilities (20-25%) (Gillberg et al., 2004; Sobanski et al., 2007; Spencer et al., 2007).

Child ADHD behaviour is a major target for clinical and health interventions seen its association with disability and adverse outcomes in later life, e.g., antisocial behaviour, relational problems, and academic underachievement (Barkley et al., 2006; Sobanski et al., 2007). According to the European clinical guidelines (Taylor et al., 2004), a variety of treatment options has been proven to be effective in reducing ADHD behaviour and improve daily functioning and long-term outcome. Based on the severity of symptoms and the presence of comorbid disorders, multimodal treatment including psychological treatment (e.g., behavioural interventions in the family and the school, parent/teacher training) and psychopharmacological treatment (stimulant or non-stimulant medication) is often indicated to modulate the behavioural expression of biological and psychological deficits that underpin the disorder.

Though the exact etiology of ADHD is currently unknown, emerging evidence suggests the involvement of genetic, neurobiological, and environmental factors. ADHD has a high heritability (on average 77%) and is associated with polymorphisms in several genes related to dopaminergic neural transmission (Spencer et al., 2007). However, gene expression seems modulated by different environmental risks (gene-environment interactions), for example prenatal smoking. Other factors associated with the development of ADHD include pre- and perinatal complications or exposure to benzodiazepines, alcohol, or stress; Family relationships and school functioning were considered as maintaining or protective factors (see Spencer et al. (2007) and Taylor et al. (2004) for more detailed

reviews). Research on underlying neurobiological/ -psychological deficits in ADHD has mainly focused on problems in executive function (such as response inhibition and working memory) (Barkley, 1997); which are postulated to be grounded in altered fronto-striatal circuits modulated by catecholamine-based neurotransmitters (Arnsten, 2009). In their review, Sonuga-Barke et al. (2010) state that such *fixed* deficit models (context- and state-independent) have been insufficient in determining cognitive impairment. They provide some alternative theories considering failures in motivational (delay aversion hypothesis; Sonuga-Barke, 2002) and energetical (state regulation deficit theory; Sergeant, 2000) systems that emphasize the *dynamic* nature of ADHD, especially the role of contextual and state factors in ADHD behaviour (Sonuga-Barke et al., 2010). Despite these significant developments in our knowledge on the pathophysiology of ADHD, there are still few examples of therapeutic and clinical innovation that build directly on these advances. This is in part due to limitations in our understanding of the significance of these (laboratory-based) ADHD deficits for everyday behaviour and functioning.

One finding from the laboratory that may have more practical resonance than others relates to evidence that behavioural symptoms fluctuate both over time and according to different environmental factors (Antrop et al., 2005a; Luman, Oosterlaan, & Sergeant, 2005; Power, 1992; Sonuga-Barke et al., 1996; Toplak & Tannock, 2005; Zentall & Zentall, 1976). Such fluctuations seen in ADHD patients have typically been explained by arousal modulation problems varying over context and time (Sergeant & Van der Meere, 1988, 1990; Sonuga-Barke, 1994, 2002; Zentall & Zentall, 1983). Arousal refers to a physiological and psychological state of being awake, aware and alert. It involves the activation of the reticular activation system (RAS) in the brain stem, the autonomic nervous system, and the endocrine system (Pfaff & Banavar, 2007; Pfaff, Martin, & Ribeiro, 2007; Schwartz & Roth, 2008; Silver & LeSauter, 2008). Previously, it has been argued that insight into the source of variability in behaviour and -relatedly- arousal provides an essential key to the understanding of ADHD (Van der Meere, 2005).

This dissertation aims at investigating the impact of *environmental conditions (Part A)* and *circadian rhythms (Part B)* on the expression of problem behaviour and arousal modulation deficits in children with ADHD when observed within their naturalistic environment. We additionally provide a neurobiological working hypothesis, including *both*

context- and circadian-dependent effects on ADHD, which may serve as a basis for future research *(Part C)*. The present chapter describes the background of this dissertation and provides an outline of the studies included.

Introducing ADHD Variability

ADHD, Arousal, and Situational Variability (Part A)

Through the years, the arousal concept in relation to environmental stimuli has gained a central place in different theoretical models of ADHD. Zentall and Zentall (1983) initially developed the theory of optimal stimulation. This neuropsychological theory states that individuals with ADHD suffer from a state of underarousal, which can be remediated by environmental stimulation. In situations with low stimulation, sensation-seeking behaviour and hyperactivity in ADHD are seen as ways to increase arousal to an optimal level. The delay aversion hypothesis (Sonuga-Barke, 1994, 2002, 2005; Marco et al., 2009) builds further on this optimal stimulation theory and states that children with ADHD work to escape or avoid the negative experience of delay, a typical situation of underarousal. It predicts that – in delay situations from which they cannot escape- children with ADHD act on the environment to alter the perception of time during the passage of delay, which results in inattentive and hyperactive behaviour. In his response inhibition/executive function deficit theory, Barkley (1997) also points to altered arousal problems, as a result of deficits in self-regulation of arousal, motivation, and affect. According to this theory, children with ADHD show an inability to control their behaviour through internal means and thus rely more on external cues to guide (goal-directed) behaviour.

Currently, the best evidence of arousal-related dysregulation in ADHD comes from studies of the impact of changing environmental context on information processes, which have been interpreted in the light of state regulation deficits using cognitive energetic models (Sergeant & Van der Meere, 1988, 1990; Sergeant, 2000). Sergeant and Van der Meere (1988, 1990) interpreted the non-optimal state of arousal as due to a problem in state regulation associated with failures to appropriately allocate effort during information processing. In this model state dysregulation refers to an imbalance between three energetic

systems that are closely linked to each other, namely effort, arousal and activation. Difficulties in state regulation in ADHD are predicted to arise not only from underarousal/activation but also due to overarousal/ activation (Sonuga-Barke et al., 2010). More specifically the authors point to the importance of 'optimal' stimulation: during fast event rate, ADHD children respond fast and inaccurate, while during slow event rate, they are expected to show slow-inaccurate responding. These findings are additionally supported by neurophysiological research describing altered responses to stimuli with different event rate in ADHD, including deviant event related potentials and heart rate variability (Borger & van der Meere, 2000; Wiersema et al., 2006). Although there is currently little research on the neurobiological correlates of this state-regulation deficit, it seems that tonic (~ baseline) activity of the locus coeruleus (LC), which is the main noradrenergic nucleus, located in the RAS of the brain stem, is associated with the regulation of arousal and several state-dependent processes, such as sensory information processing, attention, working memory, and motor processes (Arnsten & Dudley, 2005; Devilbiss & Waterhouse, 2004; Sonuga-Barke et al., 2010). Recently, an important modulating effect of the LC and noradrenergic arousal pathways on dopaminergic prefrontal cortex (PFC) function has been suggested (Arnsten & Dudley, 2005). Though research in ADHD is rather limited, the pathophysiology of ADHD appears to involve a tonic 'overdrive' of the LC, with excessive noradrenergic release leading to reduced capacity of the PFC to respond to phasic (~ specific environmental) stimuli (Mefford & Potter, 1989; Pliszka, McCracken, & Maas, 1996; Sonuga-Barke et al., 2010). This suggestion shifts the primary focus of interest from dopaminergic (Levy, 1991) to noradrenergic deficits in ADHD. The idea that state- regulation deficits are, at least in part, related to noradrenergic LC dysfunction is confirmed by several treatment modalities in ADHD, which modulate deficits in noradrenergic pathways (see Berridge & Devilbiss, 2011; Biederman & Spencer, 1999; del Campo et al., 2011; for reviews on this topic). More detailed information on state-dysregulation processes and noradrenergic LC arousal dysfunction in ADHD is provided in chapter 7.

Taken together, several ADHD models recognize an important influence of environmental conditions on the modulation of arousal levels and the expression of problem behaviour in ADHD. The validity of these theories has been confirmed in behavioural studies reporting that ADHD behaviour fluctuates according to different environmental factors such

as structure and novelty of a task or situation (Zentall & Zentall, 1976), the presence of an adult (Power, 1992), task duration (Toplak & Tannock, 2005), task event rates (Wiersema et al., 2006), reinforcements (Luman et al., 2005) and delay (Antrop et al., 2005a; Sonuga-Barke et al., 1996). However, a major limitation of these studies is that these have mainly been conducted in a laboratory setting. The relevance for everyday behaviour and functioning is less clear. Some have questioned the ecological validity of laboratory measures e.g., executive functioning tests (Barkley & Fischer, 2011): Can they really capture the complexity of real-world situations?

ADHD, Arousal, and Circadian Variability (Part B)

Up till now, time-of-day effects on behaviour and arousal modulation problems in ADHD have not been considered in the theoretical models described above. However, it is assumed that arousal variations are not only triggered by environmental stimuli but - as arousal is closely linked to sleep-wake regulation- that they are also influenced by spontaneous circadian rhythms. Circadian rhythms are 24-hour fluctuations in both physiological (e.g., body temperature, heart rate, hormone secretion) and psychological variables (cognitive performance, personality and behaviour) (Carrier & Monk, 2000; Haus, 2007; Hofstra & de Weerd, 2008; Tankova, Adan, & Buelacasal, 1994; Young, 2006), driven by the suprachiasmatic nucleus (SCN) in the ventral hypothalamus (Weaver, 1998). This biological clock has an endogenous nature, as rhythms persist even in the absence of external or environmental information. However, exogenous cues, also called zeitgebers (e.g., light), tune this biological 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 with peripheral structures takes place through both neural and endocrine factors, and enhances synchronized functioning of all different human systems, including the central nervous system, the autonomic nervous system, and the endocrine tissues (Haus, 2007). Given that these functions are implicated in arousal state regulation, arousal itself is assumed to be driven by circadian rhythms (Silver & LeSauter, 2008). Findings in animal studies confirm this connection, describing an anatomical pathway between the SCN, the biological clock, and the LC, which is an important noradrenergic nucleus in arousal

regulation (Aston-Jones, 2005). However, it must be noted that other factors are also related to arousal, including hormonal stress reactivity, emotions, temperament, and psychopharmacotherapy.

The notion of differential circadian arousal patterns in ADHD has been supported by several research domains. Briefly, there is evidence that subjects with ADHD show a higher *eveningness* preference (Caci, Bouchez, & Bayle, 2009; Rybak et al., 2007; Susman et al., 2007), more sleep-wake disturbances such as difficulties falling asleep and excessive daytime sleepiness (Boonstra et al., 2007; Cortese et al., 2009; Hvolby, Jorgensen, & Bilenberg, 2008; Lecendreux et al., 2000; O'Brien et al., 2003; Owens et al., 2009), and more hyperactivity problems in the afternoon (Antrop, Roeyers, & De Baecke, 2005b; Porrino et al., 1983; Tsujii et al., 2007; Zagar & Bowers, 1983). Findings on this research topic are however inconsistent (Corkum et al., 2001; Dagan et al., 1997; Gruber, Sadeh, & Raviv, 2000; Mick et al., 2000), so further clarification of time-of-day effects in arousal is critical to fully understand underlying mechanisms in ADHD involved in the modulation of arousal and the expression of behavioural symptoms as a function of time: Are hypo-/hyperarousal problems in ADHD particularly expressed at specific times of the day?

ADHD as a Function of Context x Time of Day: Towards Hypotheses and Future Research (Part C)

In order to determine future research directions, a more systematic approach to studying the relationship between ADHD and arousal-related variability needs to be established. With respect to environmental conditions, these effects have usually been interpreted as state regulation deficits using cognitive energetic models. Circadian effects have not been considered in these models so far. However, a role of circadian effects in ADHD is supported by two areas of well-established evidence: first, LC-arousal mechanisms are altered in ADHD leading to general difficulties in regulating physiological state in response to changing conditions as briefly addressed above (state-regulation deficit theories: Sergeant & Van der Meere, 1988, 1990); Second, LC function, as a key locus in noradrenergic pathways in the brain is implicated in arousal more generally and circadian effects specifically (Aston-Jones, 2005). Further in this dissertation, we describe in detail how

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. Based on this neurobiological working hypothesis future research recommendations will be presented (chapter 7).

A Need to Investigate Situational and Circadian Variability in ADHD

Purpose and Design of this Dissertation

In view of the considerations mentioned above, the rationale for this dissertation is based on: (i) the notion that ADHD symptoms and arousal modulation problems show fluctuations as a function of context and time-of-day; (ii) a lack of naturalistic research to explore to what extent findings related to specific ADHD deficits in response to varying laboratory task stimuli are ecologically valid ; (iii) the uncertainty whether altered circadian regulation of arousal patterns may have additional practical significance in ADHD; and (iv) the need to identify gaps in (translational) knowledge to guide further development of theories and future research in order to improve outcome and well-being in this population.

Therefore, the purpose of this dissertation was first, to investigate *situational (part A) and circadian (part B) variability* in ADHD behavioural symptoms and arousal modulation problems, and additionally, to generate a theoretical framework encompassing *both context and circadian effects,* which could guide further research developments needed to improve daily functioning in children with ADHD *(part C)*. We assume that careful observation of behaviour/arousal influencing components provides an essential key to the understanding of ADHD and its treatment.

To pursue ecological validity of findings, *in part A*, we observe elementary school children with ADHD and typically developing peers (pairs were age-, sex-, and class-matched) in their naturalistic school environment. The classroom represents an environment of choice to observe behavioural symptoms in children with ADHD since ADHD behaviour at school represents one of the most potent factors predicting school-related and broader patterns of functioning (Barkley et al., 2006; Fergusson & Horwood, 1995). Although several studies directly observed children with ADHD in their naturalistic classroom environment

(Abikoff et al., 2002; Junod et al., 2006), very few have systematically assessed the impact of different instructional conditions with varying degree of stimulation, structure, and cognitive demands (Kofler, Rapport, & Alderson, 2008; Lauth, Heubeck, & Mackowiak, 2006). Other limitations relate to, amongst others, short observation length, exclusion of significant factors such as classroom idle time and transition periods, and lack of interest in the modulating role of teachers in adapting environmental conditions to the child's needs. In the current dissertation, we examined different classroom conditions, which were hypothesized to trigger problematic behaviour in children with ADHD. More specifically, we focused on the impact of classroom idle time and different instructional contexts (i.e., class group structure, academic content types including instructional transitions, individualized teacher supervision) on classroom disruptive behaviour and task-related attention respectively. Gathering knowledge on behavioural fluctuations in ADHD under different instructional classroom conditions is important to improve educational guidelines. Classroom intervention developers may then specifically target these periods, for example by reducing triggering factors wherever possible, adapting high-risk periods to the child's needs by using alternative class group structures or increasing teacher supervision, and an optimal timing of academic lessons.

In part B, we first reviewed the current literature to gain a better understanding of the role of circadian effects in ADHD. It seemed that minor attempts have been made to evaluate time-of-day effects in cortisol and heart rate profiles in ADHD, despite the fact that the autonomic nervous system and the neuroendocrine system are major (circadian-sensitive) systems involved in arousal regulation (Pfaff & Banavar, 2007; Schwartz & Roth, 2008; Silver & LeSauter, 2008). A major limitation of previous research is limited sampling of cortisol, which is highly variable within individuals and across time-of-day. There is a consensus that intra- and interday variability in cortisol patterns call for a full circadian evaluation with multiple time points sampled on a given day across several days (Bartels et al., 2003; Houtveen & de Geus, 2009), but this methodological standard has not been applied in ADHD research. It is unknown whether circadian regulation of the autonomic nervous system is different in children with ADHD as no evaluation of 24-hour heart rate patterns is available. Therefore, we performed longer-term evaluations of heart rate and cortisol in order to detect whether time-specific alterations in arousal patterns were present

in children with ADHD as compared to their typically developing classmates. Knowledge on time–of-day effects in ADHD could lead to the adjustment of dosing and timing of ADHD medication to optimally observe and treat problematic behaviour considering its fluctuating expression. As ADHD symptoms have been explained in terms of underlying deficits in arousal modulation (both hyper- and hypo-arousal) (Sonuga-Barke et al., 2010), expertise on time-specific arousal deviations (i.e., hypo- and hyperarousal at different times-of-day) may guide specific therapeutic choices; for example, stimulant medication has predominantly been associated with an increase in arousal, therefore especially useful at times of underarousal, whereas the opposite is true for mindfulness-based interventions. If findings on disrupted circadian rhythms are being confirmed in ADHD, they would justify the (additional) use of circadian-based therapies in ADHD such as melatonin treatment and light therapy.

In part C, we developed a neurobiological working hypothesis that considers both context- and time- dependent expression of ADHD problems. This model could serve as a framework for future research on behavioural variability in ADHD to reveal critical pathophysiological mechanisms in ADHD and stimulate further development of theories, for example by disentangling more recent views on the modulating effect of LC-arousal dysfunction on PFC functioning in ADHD. Information on contextual and time-related variability of ADHD behaviour and arousal regulation problems may encourage the development of a context- and circadian sensitive protocol, which may lead to adaptations of the diagnostic setting and to a more effective evaluation of different treatment modalities, such as optimal drug dosing and timing (Chavez et al., 2009; Pelham et al., 2001; Sonuga-Barke et al., 2004; Swanson et al., 2004). Currently, variability in problem behaviour has not systematically been assessed in medication effect evaluation studies.

Outline and Research Goals

In general, this dissertation aims to investigate the impact of environmental factors *(part A)* and circadian characteristics *(part B)* in ADHD, and to develop a more interactive hypothesis for future research *(part C)*. Below we describe the subgoals addressed in each chapter of this dissertation.

With respect to environmental factors *(part A)*, we consider the following subgoals:

(i) In chapter 2, we build on the laboratory findings about the context specificity of ADHD behaviour to explore the impact of the classroom equivalent of low stimulation, low structure, and high delay settings – "idle time" - on disruptive behaviour in children with and without ADHD. We hypothesized that idle time is a common element in daily school life and that these periods exacerbate the degree of disruptive behaviours in the classroom (hyperactivity, noisiness, and disruptive social behaviour) displayed by individuals with ADHD (more than in their typically developing peers).

(ii) In chapter 3, we concentrate on classroom task-related attention in children with ADHD as a function of different instructional conditions (different class group structures and academic content types, including instructional transition periods). Given the self-regulation and motivational deficits associated with ADHD, we expected that children with ADHD would show more attention problems relative to their peers during certain conditions but not during others. Classroom inattentiveness is an important reason for clinical referral of children with ADHD and a strong predictor of their educational achievement. As the teacher is expected to play an important role in adapting contextual demands to the child's specific needs, the effect of individualized teacher supervision was additionally taken into account when explaining the relation between class context and attention.

With respect to circadian characteristics *(part B)*, we address the following subgoals:

(i) In chapter 4, we first review studies of time-of-day effects in ADHD to investigate whether the available literature supports across-the-day fluctuations in ADHD-related processes in terms of ; (i) time-of-day effects on behaviour and activity; (ii) *morningness-eveningness* chronotypology; (iii) sleep/wake rhythms; and (iv) rhythmicity in neuroendocrine and neurophysiological responsiveness. Based on these findings, it seems that a reliable way to investigate circadian arousal patterns is by a longer-term evaluation of heart rate and cortisol, which is currently not available in ADHD.

(ii)   In chapter 5, we examine whether 24-hour heart rate patterns in non-medicated children with ADHD, registered during five days, under naturalistic environmental conditions, were different as compared to normal controls. It was hypothesized that group differences in heart rate are particularly expressed at specific times of the day. Activity levels were simultaneously assessed in order to explore possible confounding effects on heart rate and to guide interpretations on the behavioural level.

(iii)   In chapter 6, we explore whether variation in cortisol levels across-the-day would be consistent with the theory of an abnormal diurnal arousal pattern associated with ADHD (i.e., time-specific hypo- vs hyperarousal). Cortisol levels in children with and without ADHD were obtained over multiple days with five measurements across each day to take into account intra- and interday variability. Since the literature suggests that ODD comorbidity may modulate these findings, two ADHD subgroups were taken into account (ADHD with and without ODD).

Considering both the environmental and circadian effects described above, we then propose a more integrative, neurobiological framework to guide future study in chapter 7 *(part C)*. Circadian effects in ADHD, along with other aspects of ADHD-related dysregulated arousal (e.g., cognitive energetic deficits) are considered to be the result of dysregulated LC function. This model highlights the potential role of LC disruption in ADHD as a biological mediator of both context specific cognitive energetic effects and context independent circadian effects. Based on this perspective, specific recommendations for future research are presented.

Finally, in chapter 8, we summarize our main findings, discuss their limitations and clinical implications, and propose some future research directions.

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Part A

Situational Variability in ADHD

Here we assess whether ADHD behaviour aggravates as a function of different classroom conditions with varying degree of stimulation, structure, and cognitive demands. In children with ADHD and typically developing classmates, we investigate the impact of classroom idle time (chapter 2) and instructional contexts (i.e., class group structure, academic content type, and individualized teacher supervision; see chapter 3) on classroom disruptive behaviour and task-related attention respectively. The identification of conditions that exacerbate problem behaviour in children with ADHD may guide the further development of teacher strategies and academic interventions.

2. The Impact of Idle Time in the Classroom:
Differential effects on Children with ADHD

Lindita Imeraj, Inge Antrop, Herbert Roeyers, Dirk Deboutte,
Ellen Deschepper, Sarah Bal, Edmund Sonuga-Barke

Abstract

Studies have identified an exacerbation of ADHD deficits under specific laboratory conditions. Less is known about the significance of such contextual factors in relation to everyday functioning in naturalistic settings. This study investigated the differential impact of classroom "idle time" -periods when students are not actively engaged or waiting for a task- on the behaviour of 31 children with ADHD (25 boys and 6 girls; aged 6-12y) and 31 sex-and age-matched normally developing classmates, who were simultaneously observed in their normal classroom during two schooldays. Both groups experienced the same amount of idle time (12% of the time). During idle time however, levels of hyperactivity and noisiness increased significantly more in children with ADHD than in their classmates (p < 0.05) highlighting the differential susceptibility of ADHD children to idle time in the classroom.

Keywords: ADHD; disruptive behaviour; classroom; context; variability

Introduction

Attention-deficit/hyperactivity disorder (ADHD; age-inappropriate and impairing levels of inattention and hyperactivity-impulsivity (American Psychiatry Association (APA), 2000)) is a high prevalence (Spencer, Biederman, & Mick, 2007), high impact disorder (Barkley et al., 2006). Laboratory studies have yielded significant advances in our understanding of the psychopathophysiology of the condition. These studies have implicated a wide range of cognitive and motivational processes (i.e., behavioural inhibition and executive functioning (Barkley, 1997), cognitive-energetic resources (Sergeant, 2000), motivational pathways and temporal processes (Sonuga-Barke, Bitsakou, & Thompson, 2010a) in ADHD. However, there are still few examples of therapeutic and clinical innovation that build directly on these advances (Sonuga-Barke, 2009). This is in part due to limitations in our understanding of the significance of these deficits for everyday behaviour and functioning. Some have questioned the ecological validity of laboratory measures of these basic deficits (Barkley & Fischer, 2011): Can they really capture the complexity of real-world situations?

One finding from the laboratory that may have more practical resonance than other relates to evidence that performance by children with ADHD varies considerably from setting to setting. In particular, individuals with ADHD seem to perform less well and their behaviour seems worse in situations with low stimulation (Antrop et al., 2000), high delay (Antrop et al., 2006), and a lack of structure (Zentall & Leib, 1985) and reward (Luman, Oosterlaan, & Sergeant, 2005). Such effects of context are consistent with a number of theories of ADHD. For instance, the delay aversion hypothesis (Sonuga-Barke, 1994) relates symptoms of ADHD to a motivational style characterized by a negative emotional reaction to the imposition of delay (Bitsakou et al., 2009; Sonuga-Barke, 1994, 2005). The theory predicts that children with ADHD learn to behave in ways that reduce the negative experience of delay; in particular by acting on the environment to alter the perception of time during the passage of delay which results in inattentive and hyperactive behaviour (Sonuga-Barke, 1994; Sonuga-Barke et al., 2010b). According to this model ADHD behaviour should be exacerbated during periods of low stimulation and delay (Antrop et al., 2002). A second relevant model is the cognitive energetic model of ADHD (Sergeant & Van der Meere, 1988, 1990). This

explains ADHD as a deficit in state regulation associated with failures to appropriately allocate effort during information processing. In this model state regulation refers to three energetic systems that are closely linked to each other, namely effort, arousal and activation. Within this framework, difficulties in state regulation can arise due to over arousal/activation and/or under arousal/activation (Sonuga-Barke et al., 2010b). The latter has previously been postulated by the optimal stimulation theory (Zentall, 1975) describing ADHD in terms of a non-optimal state of under arousal. These ADHD models recognize an important influence of environmental conditions on variations in ADHD behaviour, for example related to stimulation within and structure of these conditions. Exposed to low levels of stimulation, these theories predict that children with ADHD will show sensation-seeking behaviour in an attempt to increase arousal to optimal levels.

Since ADHD behaviour at school represents one of the most potent factors predicting school-related and broader patterns of achievement and functioning (Barkley et al., 2006; Fergusson & Horwood, 1995), the classroom represents an environment of choice to observe behavioural symptoms in children with ADHD. There have been several studies that have observed classroom behaviour in children with ADHD (Abikoff et al., 2002; Junod et al., 2006). However, only a few have identified environmental conditions that trigger and maintain problematic behaviour in ADHD (Lauth, Heubeck, & Mackowiak, 2006). Though these environmental triggers are not assumed to be causal by themselves, they may interact with specific (causal) deficits in children with ADHD (Barkley, 2007).

In this study we build on the laboratory findings about the context specificity of ADHD behaviours to explore the impact of a highly relevant classroom equivalent. One such condition –often referred to as problematic by teachers- may relate to "idle time" in the classroom, for instance when children are waiting between tasks or for the teacher to help them. These periods could be considered as waiting conditions (periods of 'delay') with typically low degrees of environmental stimulation (no task or instruction) and external structure (no directions from the teacher). Though idle time may not map exactly on these theoretical constructs, we expect that the identification of such periods may have important implications for everyday functioning of children with ADHD. Our hypothesis is that idle time will exacerbate the degree of ADHD and disruptive behaviours in the classroom displayed by individuals with ADHD. To our knowledge, only one study has attempted to link laboratory-

based measures of sensitivity to delay or low arousal settings to behaviour in the naturalistic classroom environment. Solanto et al. (2001) correlated impulsive choice patterns (preference for small immediate rewards over large delayed rewards) on a laboratory task with a range of classroom behaviours such as gross motor activity and physical aggression, highlighting the potential everyday significance of laboratory measures of delay sensitivity. A further experimental study in the naturalistic setting confirmed the view that low stimulation delay rich situations in the classroom are associated with more ADHD behaviours (Antrop et al., 2005a). Published naturalistic studies in the classroom environment have not considered idle time as such. Available data however provide support for the view that disruptive behaviour in ADHD is affected by amount of stimulation and levels of structure in the class context though findings are not always consistent (Jacob, Oleary, & Rosenblad, 1978; Lauth et al., 2006; Whalen et al., 1979; Zentall & Leib, 1985). Whereas some studies described an exacerbation of hyperactive and socially disruptive behaviour in low structure settings (Lauth et al., 2006; Whalen et al., 1979; Zentall & Leib, 1985), others reported highly structured environments to increase disruptive behaviour (Handen et al., 1998; Whalen et al., 1979). Also low stimulation classroom settings (e.g., seatwork) have been reported to increase noise-vocalization, disruptive, and off-task behaviour (Zentall, 1980). Though idle time can mostly be considered to be a classroom condition with low structure (in terms of external direction of the teacher) and low stimulation (waiting situation with no tasks or activity presented), it is not clear to what extent the findings described above (mostly referring to academic tasks-related structure/stimulation) could be generalized to this specific environmental condition (independent of academic tasks, but still within a classroom setting and not during free play).

The aims of this study therefore were to; (i) characterize the patterns of exposure to "idle time" for ADHD children and controls during an average school day, in terms of duration, and transition periods as a contributor to idle time; and (ii) examine the impact of idle time on ADHD behaviours and more general disruptive behaviour in the classroom. We predicted that children with ADHD will show more ADHD and disruptive classroom behaviours in general and that these effects will be exacerbated in the idle time condition. In statistical terms we predict a significant interaction between group (ADHD vs control) and context (idle time vs non-idle time) with the difference between idle and non-idle time being

greater for ADHD than control children. As comorbid oppositional defiant disorders (ODD) problems and academic underperformance in children with ADHD may have an impact on classroom disruptive behavior, these confounding effects were additionally taken into account.

Method

Participants

Thirty-one children diagnosed with ADHD (25 boys and 6 girls), aged 6-12 (M = 8.94; SD 1.52), were recruited from a local child psychiatric outpatient unit. Each had a formal diagnosis of ADHD combined type (DSM-IV) obtained by a clinical child psychiatric assessment (parent's history and school information). Prior to participation, diagnosis of ADHD combined type was confirmed using the Diagnostic Interview Schedule for Children, parent version (PDISC-IV) (Shaffer et al., 2000). Participants were excluded if they had an IQ less than 80 (WISC-III-R) (Wechsler, 1991), a diagnoses of pervasive developmental disorders, neurological disorders such as epilepsy, or another chronic medical condition or if they were on medication for mental health problems except for methylphenidate. Twenty-six children with ADHD took methylphenidate (17 short- and 9 long-acting formulation), but all children were free from treatment at least 24 hours prior to participation in the study. Eleven of the children with ADHD received (extra-scholarly) special education services. Controls were 31 age- and sex-matched healthy, normally developing children from the same class as the child with ADHD. These children had no medical condition and were free of medication/psychotherapy or special education classes. All children attended a regular elementary school. SES did not differ significantly between groups for mothers (χ^2 (2) = 1.07, p = 0.30) in term of highest achieved educational level.

To screen for current behavioural problems in both groups, the disruptive behaviour disorder rating scale (DBDRS) (Oosterlaan et al., 2008; Pelham et al., 1992) was filled out by parents and teachers. This questionnaire measures disruptive behaviour disorder symptoms according to the DSM criteria. Validity and reliability of the Dutch translation of the DBDRS have been proved adequate in both Dutch and Flemish children aged 6 to 12 (Cronbach's

alpha range = 0.88-0.94) (Oosterlaan et al., 2008). This 42-item questionnaire contains four child behaviour scales: inattention (9 items), hyperactivity and impulsivity (9 items), ODD (8 items), and conduct disorder (CD; 16 items). Parents rated each item on a 4-point Likert scale: from 0 (not at all) to 3 (very much). Children with ADHD were rated significantly higher than their normally developing classmates on all subscales ($p < 0.01$ for all scales) by parents and teachers respectively (inattention: M(SD) = 16.70 (6.08) vs 2.97 (3.49), 12.48 (5.95) vs 2.26 (3.08); hyperactivity/impulsivity: 15.67 (5.33) vs 2.65 (2.65), 11.00 (6.48) vs 1.65 (2.20); ODD: 9.07 (5.17) vs 1.77 (2.32), 4.71 (4.35) vs 0.55 (1.39); and CD: 2.80 (3.22) vs 0.26 (0.58), 1.55 (2.22) vs 0.10 (0.30)). Additionally, child's performance on different lesson contents was evaluated on a scale from 1 (insufficient) to 5 (well to very well) by the teacher (as included in the Teacher Report Form, TRF, Achenbach, 2001; Verhulst, van der Ende, & Koot, 1997). Children with ADHD performed less on mathematics (M (SD) = 3.43 (1.23) vs 4.30 (0.79); $p < 0.01$), language arts (3.33 (1.04) vs 4.20 (0.85); $p < 0.001$), sciences (3.46 (1.17) vs 4.44 (0.70); $p < 0.001$), but not on music and arts (3.55 (1.13) vs 3.85 (0.80); ns). As observed ADHD-related classroom behaviours may be related to comorbid ODD problems and academic underperformance rather than to ADHD as such, the ODD score of the teacher DBDRS and an 'overall' performance score (calculated as the average score on mathematics, language, and science) were included as a covariate in additional analyses.

Procedure

This study was approved by the Ethical Committee of Ghent University Hospital, Belgium. Parents of children with ADHD provided written consent and the teacher of the child with ADHD agreed to collaborate in the study. Teachers selected three sex- and age-matched normally developing classmates for each ADHD participant; they were asked to not pick their most talented or best behaved children, but those performing and behaving on average. If all parents provided written consent, one child in the control group was selected randomly to participate in the study. Prior to the observation days, teachers checked that the child with ADHD and the control child did not sit next to each other to minimze the chance of influencing each others behaviour. Observations were carried out in the classroom over two consecutive school days. Seventeen paired (ADHD and control classmate)

observations were randomly selected to be carried out on Monday and Tuesday, and 14 paired observations were carried out on Thursday and Friday. These observations took place between 2008-2010, in 30 different schools. During the observation, no specific changes (for example with respect to schedules) were required as it was designed to interfere minimally with the normal class procedures. The observers were introduced to the children as a trainee teacher, and were seated in the back of the classroom to serve the cameras during each observation. A camera was positioned in each corner at the front of the classroom to videotape the classroom environment, inclusive the behaviour of the child with ADHD and the control classmate. The children were told that these cameras helped the trainee teacher to remember class activities. On the end of the second day, the real aims of the study were revealed to the children.

Measures

Observational coding scheme

This paper is part of a broader study investigating the influence of contextual factors on ADHD symptoms. Although several standardized observation coding schemes are currently available (for a review, see Volpe et al., 2005), none contains information regarding the various factors that potentially influence classroom observations. Our coding scheme was developed specifically for this study, i.e., the Ghent University Classroom Coding Inventory (GUCCI). This inventory is partly adapted from previously published coding schemes (Abikoff, Gittelman, & Klein, 1980; Blatchford, Bassett, & Brown, 2005; Lauth et al., 2006; Milich & Landau, 1988; Porrino et al., 1983; Tsujii et al., 2007). For the purpose of this paper, we investigated disruptive behavior in ADHD as a function of context. Therefore, we considered (i) *three types of class conditions:* (i) idle time; (ii) non-idle time and ; (iii) alternative, individually assigned, activity (i.e., supplementary tasks and out-of-class activity); during which continuous codings were made for *three categories of classroom behaviours*: (i) hyperactivity; (ii) noisiness; and (iii) disruptive social behaviour (see description of variables below).

Coding procedure

Although two full school days were recorded for each child, only four observation blocks were coded using a stratification method taking into account between- and within- day effects. On one day, the first part (start of the day to playtime during morning) and the last part (playtime during afternoon to end of the day) were coded, and on the other day the second part (playtime during morning to lunch) and the third part (lunch to playtime during afternoon) of the day. Thus, together, these four blocks (two morning and two afternoon blocks) covered a whole school day across the two days combined. The mean coded observation time in the classroom was 4:34 h (SD 36:29 min). Although observation times differed between schools, observation times for the members of each dyad were similar because the child with ADHD and his matched control were observed simultaneously under the same conditions.

The Observer software

Class context categories and child's disruptive behaviour were continuously coded in The Observer (Noldus, version 9). Video material was imported in this professional software for the coding and analysis of observations. The Observer has the advantage that it can select each specific contextual condition to analyze the duration of child's disruptive behaviour (% of time) during that period. For the purpose of this study, durations of all three behaviour scores (% of time showing problematic levels of hyperactivity, noisiness, and disruptive social behaviour) were calculated during idle time and non-idle time. Supplementary tasks were not assigned sufficiently frequently to allow further analyses. During out-of-class activity, children were not visible on the film; therefore, this condition could also not be included in further analyses. The fine grained nature of the coding (continuous coding without considering fixed intervals for coding) allowed us to additionally analyze characteristics of the idle time periods such as the length of each individual episode.

Context and behavioural codings

Three class conditions were coded (button was pressed when condition began and ended); (i) idle time (e.g., the child has finished his task and is waiting for the next task to start, child is waiting for help/instructions of the teacher); (ii) non-idle time (i.e., the child is involved in a main task/activity for the whole class group) and ; (iii) alternative, individually assigned, activity (i.e., (a) a supplementary task when the child has finished the main task, e.g., silently reading a book or drawing, or (b) out-of-class activity, e.g., by going to the bathroom, delivering an out-door message for the teacher). Class conditions were mutually exclusive; The coding included separate measures for these codes for children with ADHD and controls.

During these conditions, *three categories of classroom behaviours* were continuously scored: (i) hyperactivity (no hyperactivity vs problematic levels of hyperactivity) ; (ii) disruptive non-social vocalization (no noisiness vs problematic levels of noisiness) ; and (iii) disruptive social behaviour (no disruptive social behaviour vs disruptive social behaviour). These categories were not mutually exclusive (i.e., three catgeories were coded simultaneously). A more detailed description of the GUCCI codings of disruptive behaviour variables can be found in Table 1.

As we predicted that there would be a close relation between idle time and *transition periods* (i.e., class periods just before or after playtime and periods between two different lessons), these periods were additionally coded. Transitions reflect periods of preparation and "winding up" of lessons (e.g., taking/put away pen, book, …) and are mostly a combination of non-idle time (listening to teacher instruction and carrying out the task) and idle time (when finishing the task and waiting for the next instructing or start of the lesson). Thus transitional time overlapped with the individually assigned situational codings described above: transition periods overlapped with non-idle time as the target child was carrying out the transitional instruction, and with idle time as soon as done with the instruction.

Table 1

General Description of Behaviour Codings (GUCCI)

Behaviour	Coding	Description
Activity	No problematic levels of hyperactivity	The child sits still. Little movements of fingers, hands, arms, feet or legs are tolerated as long as these are not observably annoying the teacher or disturbing their peers. The child has no difficulty sitting down and shows no gross motor movements (unless when allowed by the teacher, for example, going to the blackboard).
	Problematic levels of hyperactivity	The child shows (a) minor activity that is observably annoying/disturbing or (b) the child is not able to sit still and shows gross motor activity that is not allowed by the teacher: (i) squirms in chair, swings or overturns his chair, turns his entire trunk over each side of the chair, shows difficulty sitting down; (ii) gets out of his chair, stands up without permission; (iii) runs and climbs in the room and shows chaotic, uncontrollable behaviour. The behaviour is disruptive as it may interfere with normal class procedures, distract peers, or require instructions of the teacher to correct behaviour.
Non-social vocalization	Not noisy	Child is quite. No noisy behaviour.
	Noisy	The child shows noisy behaviour that is not socially oriented. This behaviour may be vocal/verbal or non-vocal/verbal and is not allowed by the teacher: (i) the child makes small noises such as humming, mumbling, sighing, whispering to self, ticking a pencil, ticking with fingers or feet; (ii) the child is talking to self, laughing in itself, singing, or moving chair/table; (iii) the child talks and sings loudly, and yells. The behaviour is disruptive as it may interfere with normal class procedures, distract peers, or require instructions of the teacher to correct behaviour. Unintentional behaviours such as coughing and sneezing are tolerated.
Social behaviour	Not disruptive social behaviour	The child is not interacting with peers. Alternatively, the child could interact with peers during specific tasks as expected by the teacher.
	Disruptive social behaviour	The child shows forbidden or aggressive behaviour towards peers. This could be (i) whispering or talking to peers when this behaviour was not expected by the teacher in the context of the task, or (ii) being verbally aggressive (abusing, blaming, threatening) or physically aggressive (pushing, hitting, fighting).

Note. GUCCI = Ghent University Classroom Coding Inventory; More detailed information can be obtained from the authors.

Interobserver agreement

For this study, six undergraduate psychology and medical students were intensively trained to work with Observer and supervised by the main researcher to code situational condition (one student), activity/non-social vocalization (two students), social behaviour (two students), or transition periods (one student). Observers were blind for the diagnostic status of the children. Inter-observer variability between the students and the main researcher was calculated with Cohens' Kappa for categorical variables. Based on Watkins and Pacceco (2000), agreement was excellent for idle time vs non-idle time ratings ($k = .99$), transitions ($k = .98$), hyperactivity ($k = .91$ to.97), noisiness ($k = .96$ to.99); and very good for disruptive social behaviour ($k =.74$ to $.79$).

Statistical Analyses

To investigate whether exposure to idle time differed between children with ADHD and their normal developing classmates we first calculated the proportion of each session taken up with idle time (time spent on idle time/total duration of the observation), non-idle time, and alternative activities (supplementary tasks, out-of-class activity). Groups (ADHD vs controls*)* were compared using ANOVA. Specific characteristics of idle time periods were additionally investigated: (i) duration of each interval and; (ii) transition periods as a potential contributor to idle time.

A different approach was used to assess the effect of idle time on classroom behaviours of interest (% of time showing hyperactivity, noisy behaviour, social disruptive behaviour). The dependent variables associated with classroom behaviours were not normally distributed but rather showed a Tweedie distribution (summed poisson-gamma distribution with $p = 1.5$; see supplementary material, p. 50), which refers to (i) the 'exact zeros' in our data when no disruptive behaviour was present during the observation (count data), and (ii) to the positively skewed proportions of time as soon as disruptive behaviour was present (continuous data) (Gilchrist & Drinkwater, 2000). For this reason we used generalized estimation equation (GEE) models to investigate whether the level of disruptive classroom behaviour was greater for ADHD than controls and whether this difference was exacerbated during idle time as compared to non-idle time conditions (interaction effect).

GEE takes account of the within-subject correlations present in repeated measurement data, without the covariance structure being of central interest (Zeger & Liang, 1986). Since data were correlated across conditions, GEE analyses with an exchangeable correlation working matrix were performed. Data across four observation blocks (across two days, morning vs afternoon) were averaged by the software program. In a first set of analyses, variations in disruptive behaviour levels were assessed as a function of group (ADHD vs control) and condition (idle time vs non-idle time), and the group x condition interaction was studied. Where the latter was significant we explored the nature of interaction by comparing the difference between idle and non-idle time for ADHD and control children. As the difference score was normally distributed we used ANOVA for this analysis. Cohen d effect sizes were additionally calculated (Cohen d = M_{diff} / SD_{pooled}), which are defined as small (0.20), moderate (0.50), and large (0.80). In a second set of analyses we adjusted our results for possible confounding effects by controlling our first set of analyses for the presence of comorbid ODD problems (DBDRS teacher score) and overall performance score. Supplementary activities were too infrequently coded to allow analysis. All analyses were performed in SPSS (version 19).

Results

Characteristics of Idle Time in the Class Context

Children spent, on average, 12% (SD 5%) of their time on idle time during a normal school day, which is equivalent to 32 min/day. During 83.5% (SD 8%) of their time, children were engaged in a main task or instruction (i.e., non-idle time for the sake of current analysis). During 4.5% of this time, they performed a supplementary task (2.1%; SD 5%) and were excused from the class for 2.4% (SD 3%) of their time. There was no difference between the amount of idle time experienced by ADHD and control participants (F(1,61) = 0.74; p = 0.39). Idle time intervals had a mean duration of 54 sec (SD 66 sec). Although a large number of intervals (i.e., 72%) were shorter than one minute, the smaller number of longer intervals (i.e., 28%), was responsible for 65% of the total idle time duration. Half of the idle time occurred during transition moments. During transitions, idle time was present

during 33% of the time as compared to 10% of idle time during non-transition periods. There was no difference between ADHD and control participants on any of these parameters.

Testing for Differential Effects of Idle Time on ADHD-related Disruptive Classroom Behaviour

Because of the non-normal nature of the data, median values of hyperactivity, noisiness, and disruptive social behaviour by group and condition are presented in Figure 1. For both groups, the average change in disruptive classroom behaviour ratings from non-idle to idle time condition (normally distributed) is shown in Figure 2.

When problematic levels of hyperactivity were the dependent variable, there was a main effect of group (Wald χ^2 = 17.64; $p < 0.001$) and condition (Wald χ^2 = 45.41; $p < 0.001$), and a significant interaction effect (Wald χ^2 = 5.65; $p < 0.05$). Children with ADHD showed higher levels of hyperactivity relative to their normal developing classmates. Levels of hyperactivity were higher during idle time as compared to non-idle time conditions for both groups. The interaction effect was confirmed by additional analyses of the 'change score' (ANOVA): the average increase during idle time was significantly different ($F = 4.99$; $p < 0.05$; Cohen d = 0.57) for the ADHD group (M (SD) = 9.2% (10.3%)) and for the control group (M (SD) = 4.5% (5.3%)). When noisiness was the dependent variable, there was a significant main effect of group (Wald χ^2 = 7.84; $p < 0.01$) and a significant interaction effect (Wald χ^2 = 5.79; $p < 0.05$), but no main effect of condition (Wald χ^2 = 1.47; $p = 0.23$). Children with ADHD showed higher levels of noisiness relative to their normal developing classmates. Additional analyses based on the change score confirmed that the average increase during idle time was significantly different ($F = 4.82$; $p < 0.05$; Cohen d = 0.51) for the ADHD group (M (SD) = 1.8% (4.0%)) and for the control group (M (SD) = -0.02% (3.0%)). When disruptive social behaviour was the dependent variable, the pattern was somewhat different. There was a significant main effect of group (Wald χ^2 = 4.01; $p < 0.05$) and condition (Wald χ^2 = 163.59; $p < 0.001$), but no interaction effect (Wald χ^2 = 0.96; $p = 0.33$). Children with ADHD were more socially disruptive than their peers (M_{diff} (SD_{pooled}) = 2.1% (4.0%)). Both groups showed more of this behaviour during idle time as compared to non-idle time conditions (M_{diff} (SD_{pooled}) = 11.6% (3.8%)).

Figure 1. Median values of hyperactivity, noisiness, and disruptive social behaviour by group and condition
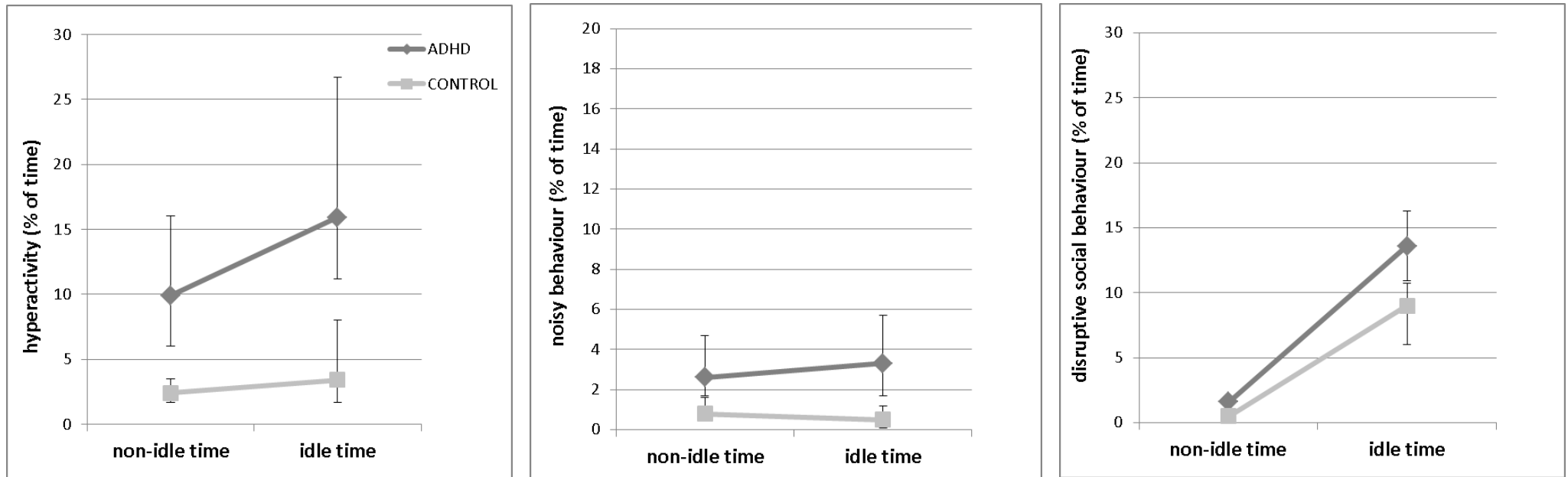
Note. Median values were presented as behavioural ratings were positively skewed. Error bars represent the semi interquartile range.

Though higher ODD problems were associated with higher levels of hyperactivity (trend effect: Wald χ^2 = 2.99; p = 0.08) and disruptive social interactions with peers (significant effect: Wald χ^2 = 3.82; p < 0.05), controlling for ODD problems in the main analyses did not alter the pattern of any of the previously reported results. When included in the models above, academic performance score did not significantly contribute to variations in disruptive behavior levels and did not alter our main findings.

Figure 2. The average change in disruptive classroom behaviour from non-idle to idle time condition by group.
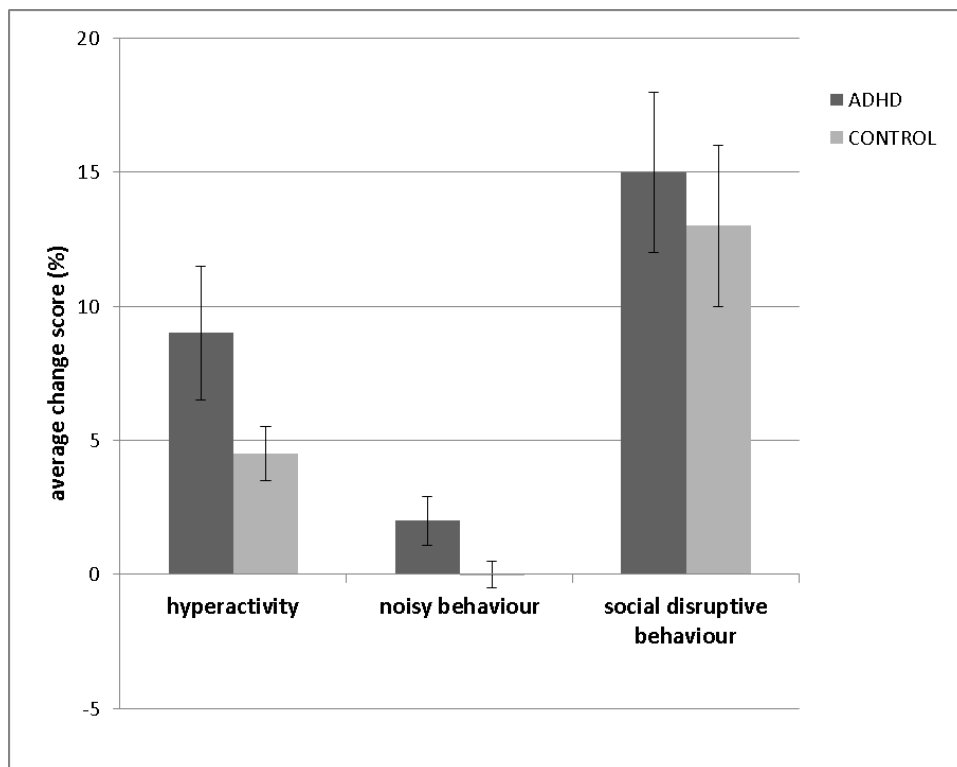
Note. Error bars represent the 95% confidence interval.

Discussion

Laboratory studies have shown that ADHD children's disruptive behaviour and performance deteriorates in certain contexts (Antrop et al., 2000; Antrop et al., 2006; Zentall & Leib, 1985). These setting-specific effects are predicted by a number of theories of ADHD – especially those that emphasize the role of context-dependent dynamic processes in ADHD pathophysiology (Sonuga-Barke et al., 2010a). However, little is understood about the

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practical implications of context effects on everyday behaviour and functioning in naturalistic environments (Lauth et al., 2006). Given the artificial nature of the laboratory environments it is not clear that these effects will generalize to the real world (Barkley & Fischer, 2011). The current study tested the prediction, derived from these observations and theories, that idle time (e.g., when the child is between tasks or when waiting for help from the teacher) would have a greater impact on the behaviour of children with ADHD than non-ADHD classmates. To do this we recorded the amount of idle and non-idle time in a typical school day (in fact over two days) and then measured three target behaviours during these periods.

There were a number of findings of interest. First, all children appeared to spend a surprising amount of their school day in the classroom confronted by idle time. Considering that this environmental condition is expected to be a risk factor in triggering and maintaining disruptive behaviours, it was worthwhile to explore its effects in the classroom. Second, unexpectedly children with ADHD were not exposed to more idle time than were their non-ADHD class mates. We initially assumed that children with ADHD would finish their tasks sooner based on their impulsive style. One possibility is that inattention problems may prevent them from finishing their tasks (high degree of off-task rather than idle time) as described in the DSM-IV criteria (APA, 2000). On the other hand, despite their putative aversion for delay situations (Sonuga-Barke et al., 2008), it appeared that children with ADHD nor their teachers could reduce the amount of idle time exposed to as compared to their peers, for example by shifting to alternative class activities. Third, not surprisingly, ADHD children displayed higher levels of each of the three measured categories – hyperactivity, noisiness and inappropriate social behaviour- irrespective of setting. In general, the classroom is a setting requiring high levels of self-regulation (Barkley, 1997), motivation (Sonuga-Barke, 2005), and cognitive and information processing skills (Sergeant, 2000) and is likely to be especially demanding for ADHD children who often have deficits in these domains (Abikoff et al., 2002; Junod et al., 2006). This finding of group differences also validated the coding system developed for the study. Fourth, for two of the target behaviours, there was a general effect of idle time on behaviour – hyperactivity and inappropriate social behaviour. Even non-hyperactive children engaged in potentially disruptive behaviour during these periods when there is no specific task to perform. Finally,

in the case of hyperactivity and noisiness, as predicted, it did appear that idle time had a differential impact on ADHD children and their classmates. These findings are consistent with laboratory tasks; a different pattern of increased activity levels has previously been reported in non-choice conditions (waiting situations from which children could not escape) (Bitsakou et al., 2009; Sonuga-Barke, 1994, 2005). However, in their semi-experimental classroom observation, Antrop et al. (2005a) reported a similar effect of waiting on both groups in terms of increased activity (only 14 children were observed in each group). They reported "additive" effects indicating that children with ADHD experience more difficulties within the idle time condition relative to control children or relative to non-idle time conditions.

From a practical perspective differential effect of idle time may have a substantial impact on everyday functioning of ADHD children as we showed that children in general are exposed to this condition for substantial proportion of lesson time, (i.e., 12% for both ADHD and normal developing peers). The failure to engage effectively in, and operate efficiently in, a delay-rich environment may reduce the development of organizational skills and strategies (Sonuga-Barke, 2005), which over time contributes to academic failure in children with ADHD (Fergusson & Horwood, 1995). Although the majority of idle time periods was very short (< 1 min), the longer periods (≥ 1 min), were still responsible for two thirds of total idle time. Furthermore exposure to idle time seems to be associated especially with transition periods (i.e., class periods before or after playtime and between different tasks). During these vulnerable time periods, children spent one third of their time exposed to idle time (i.e., waiting for the next instruction or for the task to start). Previously, Antrop, Roeyers, and De Baecke (2005b) reported an increase in hyperactive behaviour after playtime in the afternoon. It is unclear whether this rise is due to the transition period as such or to delay periods associated with it. In either way, these transition-idle time moments are a primary focus of concern and represent a good candidate target for intervention. The special structuring of classroom transitions, for example, has been proven to be an effective way of reducing disruption (Lee, 2006).

In the case we consider idle time to be a relevant classroom equivalent for laboratory conditions related to high delay (i.e., waiting situation), low structure (in terms of external direction of the teacher) and low stimulation (waiting situation with no tasks or

activity presented), from a theoretical perspective findings may be consistent with a number of different models of ADHD. These models emphasize the role of environmental conditions on ADHD behaviour, for example the delay aversion hypothesis (Sonuga-Barke, 2005), the optimal stimulation model (Zentall, 1975) and state regulation deficit model (Sergeant, 2000). In terms of the delay aversion model this effect of idle time can be explained in terms of the negative emotional reaction in children with ADHD to the imposition of delay (Bitsakou et al., 2009; Sonuga-Barke, 1994, 2005). When these children are exposed to waiting situations (with low stimulation) which they cannot 'escape' from, ADHD behaviour is exacerbated (Antrop et al., 2002) in an attempt to reduce the negative experience of delay (Sonuga-Barke, 1994; Sonuga-Barke et al., 2010b). In terms of the optimal stimulation model children with ADHD will show sensation-seeking behaviour (for example hyperactivity) when confronted with low stimulation conditions such as idle time, in an attempt to increase their non-optimal arousal levels. In terms of state regulation deficit model failures to properly regulate energetical state (arousal/activation) become obvious when challenged to do so in non-optimal settings such as conditions with low stimulation and slow event rate (Sonuga-Barke et al., 2010b).

Previous naturalistic observational studies have reported differences in behaviour as a function of structure and stimulation; though these did not consider idle time as such. Some of them found differential patterns in children with ADHD with respect to hyperactivity during in-seat versus out-of-seat lessons (Porrino et al., 1983; Tsujii et al., 2007), social interactions during self-paced activities versus externally-paced ones (Whalen et al., 1979), and daydreaming in a formal (academic) versus an informal setting (Jacob et al., 1978). Other authors described comparable effects in both groups rather than differentiating between ADHD and control: for example, both children with and without ADHD were reported to show more disruptive behaviour in non-instructional or self-paced settings (Lauth et al., 2006; Zentall & Leib, 1985) and during low stimulation (Zentall, 1980). However, it must be noted that these studies included a smaller sample size, shorter observation periods, and different operationalization as compared to this study. Though we found a differential exacerbation during idle time for hyperactivity and noisiness, with respect to social disruptive behaviour the increase during idle time was similar for both groups. It is possible that during idle time situations, the "true" nature of a child's behavior

tends to emerge, and for *all* children this seems to include an increase in socially disruptive behavior, whereas only *some* children will show an increase in hyperactivity. Explanatory theories of ADHD may therefore relate to core ADHD behaviour rather than less central facets of the condition. Either way, it seems reasonable to assume that the idea of what is expected to be a normal activity level will be exceeded more easily in children with ADHD. This kind of behaviour is highly relevant as these extreme levels of disruptive behaviour will never occur in control children in any situation.

Although this study concentrated on classroom behaviour, it would be plausible that similar effects play a role in other everyday environments. In a diagnostic setting for example, this finding can explain the clinical observation that children with ADHD suffer when they are confronted with waiting in unstructured settings. Observations of the child in the waiting room or during experimentally-induced idle time periods during consultations may reveal ADHD behaviour that might be not obvious in a one-to-one interaction within a non-familiar clinical context (Power, 1992; Zentall, 1975). We assume that also waiting situations at home may be a target of interest if willing to reduce disruptive behaviour problems in children with ADHD. Parents should be advised to anticipate the challenges of transition and idle time situations by for example proposing short alternative activities.

This study had a number of strengths especially relating to its naturalistic observational study, its sampling over large periods of the day using a reliable coding scheme and the relatively large sample of patients. There were some limitations. First, the naturalistic class environment represents a less-standardized, less-controlled setting as compared to the laboratory context. It was not possible to control for every aspect of stimulation or structure within the environment; for example, the effect of the camera, the presence of the examiner, additional noise, and unexpected interference. As the child with and without ADHD were observed simultaneously in the same classroom, it is reasonable to assume that these effects were similar for both children. Second, despite the ecological nature of our observations, findings may not generalize to all settings and all school days (Hintze & Matthews, 2004). Current findings relate to Flemish regular elementary classrooms and may therefore not be representative for other world parts or special education settings. Third, we considered idle time (periods when children were between tasks or waiting for instructions) to be a relevant classroom equivalent of laboratory settings

with high delay, low stimulation, and low structure settings, but this measure may not map exactly on these theoretical constructs. Moreover, non-idle time may include times when students were involved in unstructured or low stimulation tasks. Despite these overlap in terms of these features, the current operationalization seemed highly relevant and practically useful in children's everyday classroom environment. Fourth, as children with ADHD may face motivational problems and aversive feelings towards academic tasks, classroom idle time may be a welcome break rather than an aversive challenge. However, we expect that these children do not choose to have an idle time period, but prefer to shorten the period of delay as suggested by several laboratory tasks. Though the choice for sooner-smaller rewards is more pronounced when trial and task length can be reduced (Marco et al., 2009), other authors failed to support these findings (Scheres et al., 2006). Whereas ADHD has been related to increased sensitivity to delay before rewards (Tripp & Alsop, 2001), the delay aversion hypothesis as initially described by Sonuga-Barke et al. (1992) does not distinguish between pre- or post reward delays.

In sum, this study found that idle time in the classroom had a significant effect on behaviour in the classroom, eliciting more potentially disruptive behaviours. For hyperactivity and noisiness, these effects were exacerbated more for children with ADHD as compared to their peers. Classroom interventions might consider targeting specifically these periods to improve academic performances and social and emotional well-being especially in children with ADHD (Antrop et al., 2005a; Hoff & DuPaul, 1998).

Acknowledgements

Supplementary material

Illustration 1. Tweedie density function with p = 1.5 (continuous data with exact zeros)
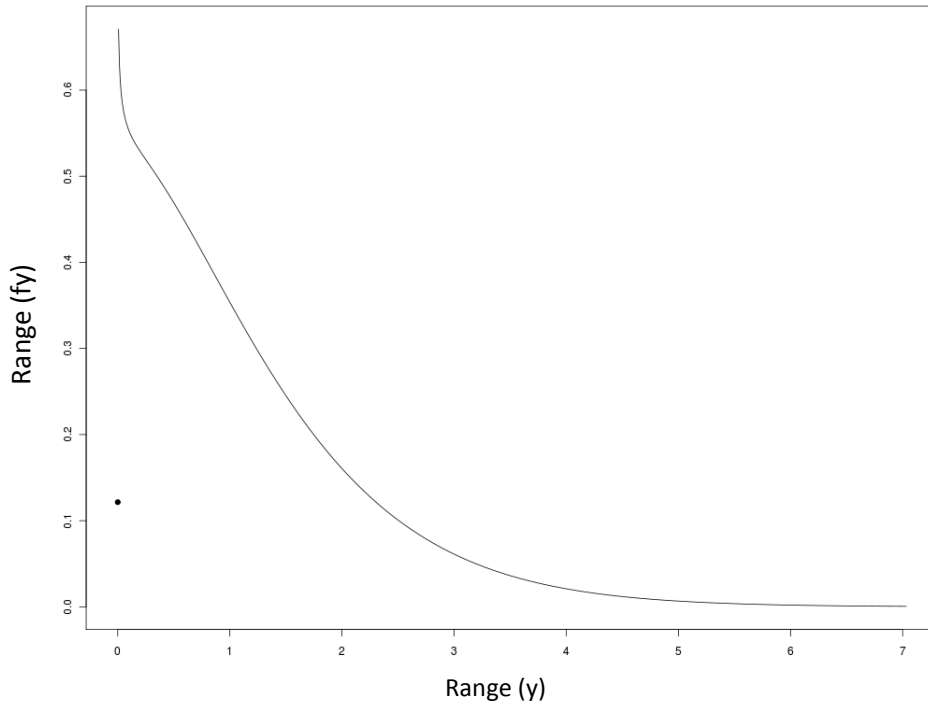
Note. The polygons indicate the discrete probability of Y = 0 when $1 < p < 2$.

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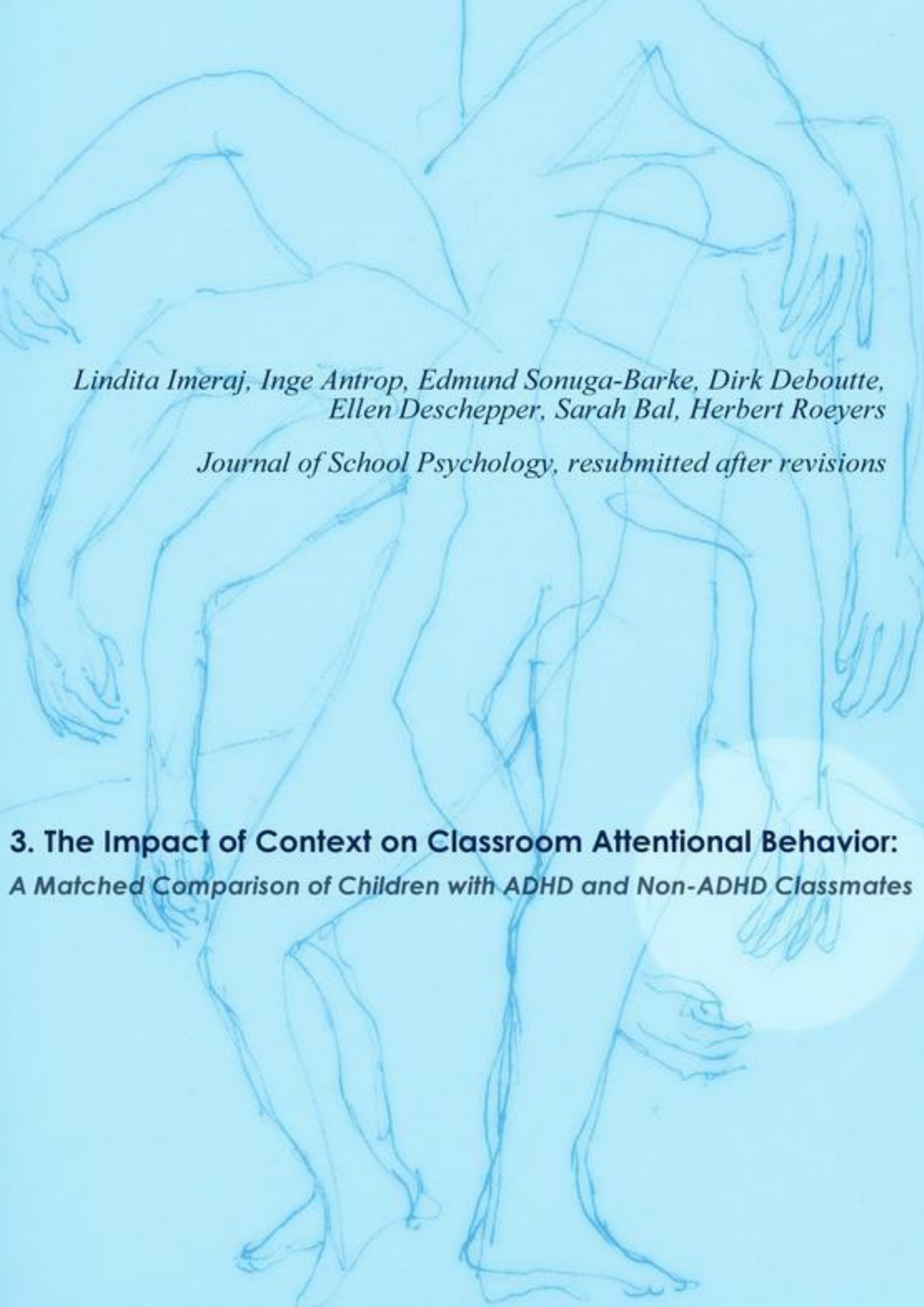
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Lindita Imeraj, Inge Antrop, Edmund Sonuga-Barke, Dirk Deboutte,
Ellen Deschepper, Sarah Bal, Herbert Roeyers

3. The Impact of Context on Classroom Attentional Behavior:

A Matched Comparison of Children with ADHD and Non-ADHD Classmates

Abstract

Classroom inattentiveness is an important reason for clinical referral of children with ADHD and a strong predictor of their educational achievement. This study investigates academic attentional engagement of children with ADHD in the classroom as a function of instructional context. Thirty-one pairs of children (one with ADHD and one age-and sex-matched control (25 boys and 6 girls; aged 6-12y)) were observed in their classroom environment during two consecutive schooldays. Attentional behavior (time on-task, attention span) of ADHD and non-ADHD individuals was compared in different class contexts (i.e., different class group structures and academic content types). Individualized teacher supervision was simultaneously assessed. Generalized Estimation Equation (GEE) analyses showed that children with ADHD were less on-task ($p<0.05$) than controls during individual work and whole class group teaching, but not during small group work; and had shorter attention span ($p<0.05$) during academic tasks (mathematics/language and sciences) and instructional transitions between tasks, but not during less academic tasks (music/arts). These effects persisted even after controlling for the higher levels of teacher supervision observed for ADHD pupils across all contexts ($p<0.01$). Findings provide evidence that despite receiving more 'overall' teacher supervision, children with ADHD displayed lower levels of attention in settings that place high self-regulatory, information-processing, and motivational demands on them. This raises questions about the suitability of the normal classroom (with additional supervision) as an optimal learning environment for children with ADHD.

Keywords: ADHD; attentional behavior; class observation; situational variability; teacher supervision

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common child psychiatric disorders characterized by age-inappropriate and impairing levels of inattention and hyperactivity-impulsivity (APA, 2000). Though these symptoms are considered to be persistent across various contexts, they are also exacerbated in some settings. The school classroom, for instance, has been identified as a primary setting for the expression of problematic behaviors in ADHD (Abikoff et al., 2002; Junod et al., 2006). Indeed it is not surprising that high educational demands in this setting are challenging for children with ADHD considering the self-regulation/executive function (EF) (Barkley, 1997) and motivation (Sonuga-Barke, 2005) deficits associated with the condition.

Failures of academic engagement represent one of the most potent predictors of school achievement and broader patterns of functioning in ADHD (Barkley et al., 2006; Fergusson & Horwood, 1995). Indeed from an educational perspective, pupils with ADHD are often first referred because of difficulty in attending appropriately to educational tasks and exercises (Pelham, Fabiano, & Massetti, 2005). Though deficits in EF (e.g., response inhibition, planning, sequencing, motor control, and selective attention) have been shown to predict ADHD-related academic underperformance, it has been suggested that ADHD behaviors (in particular attention) were even a stronger predictor of performance than EF (see review of (Daley & Birchwood, 2010). A recent meta-analytic review by Kofler et al. (2008) of 23 direct observation studies confirms significant classroom inattentiveness in children with ADHD: On average they were able to focus their attention in classroom settings approximately 75% of the time compared to 88% for typically developing peers. Though these effects were obtained across a broad range of settings, the authors highlight the association between ADHD and high levels of variability in levels of attention to academic tasks: A finding in line with previous reports of inter- and intra-day variability of ADHD symptoms (Abikoff et al., 2002; Castellanos et al., 2005; Imeraj et al., 2012) Relatedly, on-task behavior can be seen as the product of an interaction between child characteristics and environmental constraints and demands (Baker et al., 2008).

To date, variability in attention to task in ADHD has mainly been investigated by measuring performance during laboratory tasks. Such research mostly focuses on

neuropsychological features (e.g., reaction times) and physiological variables (e.g., heart rate variability). These facets appear to be highly context dependent. Situational factors that reduce attention to task and reduce performance include; the absence of an adult observer (Power, 1992), long task duration (Toplak & Tannock, 2005), lack of rewards (Luman, Oosterlaan, & Sergeant, 2005) and delay (Antrop et al., 2006; Sonuga-Barke et al., 1996). Though deficits in performance and EF seen under strict laboratory conditions are common in ADHD (Daley & Birchwood, 2010), findings seen under such conditions may not generalize to the situational dynamics of everyday life in the classroom. Several authors indicate the need to consider children's on-task behavior within the naturalistic classroom environment to fully understand the nature of academic engagement problems and the situational factors that moderate it (Kofler et al., 2008).

Despite several direct observational studies of children with ADHD in their ecological classroom environment (Abikoff et al., 2002; Junod et al., 2006; Rapport et al., 2009), few studies have systematically assessed the impact of different classroom contexts, settings and tasks to influence attentional behavior in ADHD (Kofler et al., 2008; Lauth, Heubeck, & Mackowiak, 2006). Of those studies that have looked at this, notwithstanding the fact that definitions of different contextual conditions vary considerably between studies, data generally support the view that attentional behavior in children with and without ADHD is affected by context (Lauth et al., 2006; Whalen et al., 1979). However, findings are inconsistent with regard to specifics. On the one hand, similar contextual effects on both ADHD and non-ADHD groups of children have been described: Some authors reported negative behavior in all children during highly structured activities, for example, an exacerbation of off-task behavior during whole class teaching (teacher-initiated structure) as compared to group and individual work conditions (higher student self-determination/pacing) (Lauth et al., 2006; Zentall, 1980); whereas others noted that more structured academic environments can also generate positive effects in classroom behavior such as higher compliance with tasks (Beck et al., 1999); while more self-paced activities yield both more on-task and out-of-seat behavior (Lauth et al., 2006; Zentall, 1980). On the other hand, differential effects of context on children with and without ADHD have been observed. Jacob, O'Leary, and Rosenblad (1978) reported more daydreaming in children with ADHD in a formal setting as compared to controls, but not in an informal setting. Similarly,

higher on-task behavior was found in children with ADHD (Hart et al., 2011) and those at risk for disruptive disorders (Baker et al., 2008) during cooperative learning in small class groups as compared to individual work and whole class group teaching.

One explanation for the reported inconsistencies may relate to the presence of concurrent teacher supervision. For example, small group settings may have beneficial effects as they combine the presence of high levels of structure as well as the opportunity for one-to-one teacher supervision (Baker et al., 2008). Though individual supervision is also more likely during individual work, the latter may place higher self-regulatory demands on the child with ADHD, which may be especially challenging for them. In this sense teachers seem to play an important role in adjusting the classroom environment to the specific needs of the child at risk for learning problems and to encourage classroom attention in different instructional settings (Baker, 2006; Baker et al., 2008). Despite well-known benefits of one-to-one supervision in general on vigilance of children with ADHD (Power, 1992), studies have not, to date, assessed individual teacher supervision across instructional settings in this population. Another possible explanation for this inconsistency is the limited number of settings in which children were observed in previous studies. Most studies focused on academic tasks such as maths and language (Lauth et al., 2006), excluding less academically-oriented class activities (such as music and arts) as well as instructional transition periods between lessons. Attention levels across these different lesson types are however likely to be influenced by degree of motivation and/or levels of difficulty and academic underperformance (Whalen et al., 1978).

Finally, studies have some methodological limitations that may account for discrepancies in results. For example, most studies observed children's behavior during short periods within one day and so their observations may lack reliability and generalizability, in particular because they were unable to control for the confounding type of different instructional settings (Kofler et al., 2008). In addition, studies have rarely employed a level of detail in their observation that would allow the assessment of the duration of each on-task episode. We know of only one study that has investigated classroom attention on a more microscopic level in children with ADHD in an ecologically valid classroom setting (Rapport et al., 2009). The authors found that the children with ADHD remained attentive for shorter durations and switched states more frequently relative to typically developing children.

Based on this study, it was not clear whether different instructional effects within the classroom context would influence the expression of such problems.

The aim of this study is to investigate the impact of instructional context on levels of attention-related behaviors among children with ADHD and their normal developing classmates. To address the limitations in previous studies, we included a wider variety of class context conditions i.e., class group structure and academic content (inclusive instructional transition periods) and a range of levels of teacher supervision. Confounding effects of academic performance on task behavior were additionally explored. From a methodological view, observations were taken across the whole school day on two separate days in order to capture a variety of settings. A more detailed coding allowed the measuring of not only children's overall percentage of time spent on-task but also duration of each on-task interval (referred to as attention span). We formulated the following research questions:

(i) Are attentional problems in the classroom (as measured by on-task levels and attention span) exacerbated in children with ADHD in specific class context conditions, i.e., (a) with respect to specific class group structures, and (b) with respect to academic content area (inclusive instructional transition periods). Our prediction was that children with ADHD will generally display lower levels of on-task and shorter attention span; and that whole class group teaching, highly academic lessons, and transition periods will challenge attention in all children, but particularly in those with ADHD. In statistical terms we predict a significant interaction between group and context conditions even after controlling for academic underperformance in this group.

(ii) Has the teacher's supervision levels an important role in explaining the relation between class context and attentional behavior? Based on the literature we expect that teachers may adapt their levels of supervision to class context and the child's specific needs in order to enhance attention. This will influence the interaction between context and group described in (i). To better understand the basis of this relation we investigated whether (a) class context conditions have an impact on the amount of individual teacher supervision in children with and without ADHD, and (b) irrespective of context, whether levels of teacher supervision are related to attentional behavior in both groups? We assumed that, in general,

one-to-one teacher supervision will be more common in the individual and small group conditions compared to the whole class group condition, but that these teacher practices may particularly affect students with ADHD. We also hypothesized that higher levels of teacher supervision will be associated with better academic engagement, but this effect may be different in children with and without ADHD.

Method

Participants

Thirty-one children diagnosed with ADHD (25 boys and 6 girls), aged 6-12 (M = 8.94; SD 1.52), were recruited from a local child psychiatric outpatient unit. Each had a formal diagnosis of ADHD (DSM-IV-TR) obtained by a clinical child psychiatric assessment. A multidisciplinary approach was employed including a parental history of child's symptoms as well as information from teachers (and if necessary a school observation), a neuropsychological evaluation, and a medical assessement. Prior to participation, a structured interview for parents (Diagnostic Interview Schedule for Children, PDISC-IV) was used to confirm the clinical diagnosis of ADHD-Combined Type (Shaffer et al., 2000). Only children with ADHD combined type were included to increase homogeneity of the sample. Participants were excluded if they had an IQ less than 80 (WISC-III) (Wechsler, 1991), a diagnosis of pervasive developmental disorder, a neurological disorder such as epilepsy, or another chronic medical condition; or if they were on non-stimulant or other psychotropic medication (e.g., for anxiety, depression), except for methylphenidate. Twenty-six children with ADHD were taking methylphenidate (17 short- and 9 long-acting formulation), but all children were free from treatment at least 24 hours prior to participation in the study. This was verified with the parents and teacher on the first observation day. Control participants were 31 age- and sex-matched healthy, normally developing children from the same class as the child with ADHD. These children had no medical condition and were free of medication/psychotherapy or special education classes. All children attended a regular elementary school. SES did not differ significantly between groups in terms of mothers (χ^2 (2) = 1.07; ns) in term of highest achieved educational level achieved by mothers.

To screen for current behavioral problems in both groups, the disruptive behavior disorder rating scale (DBDRS) (Oosterlaan et al., 2008; Pelham et al., 1992) was filled out by parents and teachers on the first observation day. This questionnaire measures disruptive behavior disorder symptoms according to the DSM criteria. Validity and reliability of the Dutch translation of the DBDRS have been proved good to excellent (Cronbach's alpha range = 0.88-0.94) for both Dutch and Flemish children aged 6 to 12 (Oosterlaan et al., 2008). This 42-item questionnaire contains four child behavior scales: inattention (9 items), hyperactivity and impulsivity (9 items), ODD (8 items), and CD (16 items); Each item was rated on a 4-point Likert scale: from 0 (not at all) to 3 (very much). Children with ADHD were rated significantly higher than their normally developing classmates on all subscales ($p < 0.01$ for all scales) by parents and teachers respectively (inattention: M(SD) = 16.70 (6.08) vs 2.97 (3.49), 12.48 (5.95) vs 2.26 (3.08); hyperactivity/impulsivity: 15.67 (5.33) vs 2.65 (2.65), 11.00 (6.48) vs 1.65 (2.20); ODD: 9.07 (5.17) vs 1.77 (2.32), 4.71 (4.35) vs 0.55 (1.39); and CD: 2.80 (3.22) vs 0.26 (0.58), 1.55 (2.22) vs 0.10 (0.30)).

Procedure

This study was approved by the Ethical Committee of Ghent University Hospital, Belgium. Parents of children with ADHD provided written consent and the teacher of the child with ADHD agreed to collaborate in the study. Teachers (n = 31) were aware that this study investigated differential effects of classroom contextual factors on behavior in children with and without ADHD. They were however blind to the specific factors assessed (for example, they did not know that individual teacher supervision was being assessed) and specific hypotheses of the study. Teachers selected three sex- and age-matched normally developing classmates for each ADHD subject; and were asked to not pick their most talented or best behaved children, but those performing and behaving in an average way. If all parents who were approached provided written consent, one child in the control group was selected randomly to participate in the study (31 control children were picked from a total of 65 who had consent forms). Prior to the observation days, teachers checked that the child with ADHD and the control child did not sit next to each other to minimalize the chance of influencing each others behavior. Thirty-one paired (ADHD and control classmate)

observations were carried out in 31 different classrooms over two consecutive school days in order to capture different instructional context conditions. During the observation, teachers were not required to introduce specific changes to classroom activity (for example with respect to schedules) to minimally interfere with the normal class procedures. The observer was introduced to the children as a trainee teacher, and was seated in the back of the classroom to serve the cameras during each observation. A camera was positioned in each corner at the front of the classroom to videotape the classroom environment, inclusive the behavior of the child with ADHD and the control classmate. The children were told that these cameras helped the trainee teacher to remember class activities. On the end of the second day, the real aims of the study were revealed to the children.

Measures

Direct Observation

Despite the fact that observational research is time-consuming, labour- intensive and therefore has a high financial cost, direct observation of children with ADHD in their ecological setting is recommended (Antrop et al., 2005): (1) laboratory findings are seldom representative for the home and school situation (Antrop et al., 2000; Danforth, Barkley, & Stokes, 1991; Tryon, 1993; Zentall & Zentall, 1976), (2) behavior is more variable when observed within this context (Tryon, Pinto, & Morrison, 1991), and (3) ADHD behavior is particularly expressed within a familiar environment rather than in situations that provoke novelty or fear (Teicher et al., 1996; Zentall, 1975). Measuring and quantifying behavior can allow us to reliably estimate and compare across children and settings, and to determine the extent to which other factors influence it (Kofler et al., 2008). However, the generalizability of systematic direct observations across time and setting has been thoroughly discussed. For example, Hintze and Matthews (2004) concluded in their study that adequate reliability could not be achieved with respect to on-/off-task behavior after observing students twice a day (15 min; 60 sec interval) over a course of two weeks. These authors make the following suggestions: (i) fewer observations of longer duration should produce more reliable estimations of behavior; (ii) observing in more settings might capture a more accurate representation of behavior; and (iii) on-/off task behavior might be a more complex

construct requiring definitions and coding intervals that can capture the nature of behavior in all its complexity.

Observational coding scheme

This paper is part of a broader study investigating the influence of contextual factors on ADHD symptoms; another study on the impact of classroom idle time on disruptive behavior in children with and without ADHD is currently under review. Although several standardized observation coding schemes are currently available (for a review, see Volpe et al., 2005), none contain information regarding the various factors that potentially influence classroom behaviors. Our coding scheme was developed specifically for this study, i.e., the Ghent University Classroom Coding Inventory (GUCCI). This inventory is partly adapted from previously published coding schemes (Abikoff, Gittelman, & Klein, 1980; Blatchford, Bassett, & Brown, 2005; Lauth et al., 2006; Milich & Landau, 1988; Porrino et al., 1983; Tsujii et al., 2007). A more detailed description of the GUCCI codings can be obtained from the corresponding author. For the purpose of this paper, we investigated attention to educational tasks and activities in ADHD as a function of instructional context. Therefore, we considered (i) three types of class group structures and (ii) four academic content types during which continuous codings were made for; (i) child's attentional behavior and (ii) teacher's supervision of the child (see description of variables below).

Coding procedure

For coding, four blocks (two morning and two afternoon blocks across two days) were selected to cover a whole school day across both of the two days; to capture a large variety on contextual conditions. More specifically, the four observation blocks were selected using a stratification method taking into account between- and within- day effects. On one day, the first part (start of the day to playtime during morning) and the last part (playtime during afternoon to end of the day) were coded, and on the other day the second part (playtime during morning to lunch) and the third part (lunch to playtime during afternoon) of the day. The mean observation time was 4:34 h (SD 36:29 min). Although observation time differed between schools, observation times for the members of each dyad were similar because the child with ADHD and its matched control were observed simultaneously under the same environmental conditions.

Observer software

Class context categories, child's on-task behavior, and teacher supervision were continuously coded in Observer (Noldus, version 9). Video material was imported in this professional software for the coding and analysis of observations. Observer has the advantage that it can select each specific contextual condition to analyze the duration of child's on-task behavior (% of time on-task) and the individual teacher supervision received during these periods. The fine grained nature of the coding (continuous coding without considering fixed intervals for coding) allowed us to additionally analyze more microscopic attentional processes such as the length of each individual attention interval (i.e., attention span, which is on its turn inversely related to the number of shifts between attention/non-attention).

Class context variables (independent variables)

We assessed (i) *three types of class group structures*, i.e., (a) whole group work (teacher gives instructions to or teaches the whole class group), (b) small group work (children are instructed to work in small (less than six students) cooperative learning groups; they are required to work as a team and actively interact to accomplish a task), and (c) individual work (students work individually without ongoing whole-group teacher instructions, for example individual reading, completing worksheets) and (ii) *four academic content types,* i.e., (a) highly academic lessons (mathematics and language), (b) academic lessons (sciences), (c) non-academic lessons (music and arts), and (d) instructional transitions. The latter reflected class periods just before or after playtime and periods between two different lessons. Instructional transitions were periods of preparation and "winding up" of lessons (e.g., taking/put away pen, book, …) and are mostly a combination of instructions (listening to teacher instruction, carrying out the task, and -when finishing the task- waiting for the next instruction or start of the lesson). The two main coding categories overlapped, but conditions within each category were mutually exclusive. Contextual codings for the child with ADHD and its matched control were carried simultaneously.

Child behavioral variables (dependent variables)

Child's attentional behavior was continuously coded as on- vs off-task. On-task behavior was scored when children were involved in those class activities "expected" by the teacher, for example listening to teacher, doing an assignment, follow-up instructions. Consistent with existing direct observation studies, the current study based the scoring of attention/on-task behavior on whether visual attention to required stimuli was present. Off-task behavior was operationalized as being involved in activities "not expected" by the teacher (e.g., day-dreaming, doing something else), unless the child was engaged in an alternative task-appropiate behavior allowed by the teacher (e.g., sharpening a pencil). For further analyses, with the Observer software, we calculated (i) the proportion of time spent on-task during each contextual condition (on-task duration / total duration of the interval considered), and (ii) the mean on-task interval duration (referred to as attention span; sum of all individual on-task durations / number of times on-task occurs during the interval considered).

Teacher supervision (used as dependent and independent variable)

Similarly, codings were made for individual teacher supervision of the child (absent vs present). Teacher's supervision was coded as present when children were individually interacting with the teacher, for example when the child was communicating with the teacher or when he/she was receiving one-to-one supervision or feedback. When the child was part of the group as a whole, for example the child was listening to the teacher without a "one-to-one interaction", individual teacher supervision was considered to be absent. For further analyses, we calculated the proportion of time the child received individual teacher supervision during each contextual condition or during the observation as a whole (considering supervision as the dependent vs independent variable, respectively).

Interobserver agreement

Five undergraduate psychology and medical students were intensively trained to work with Observer and supervised by the main researcher to code class group structure/academic content type (one student), on-task behavior (two students), teacher's supervision (two students). Observers were blind to children's diagnostic standing. Interobserver variability between the students and the main researcher was calculated with Cohens' Kappa (nominal variables). Based on Hintze and Matthews (2004), agreement was excellent for class group

structures (k = 0.99), academic content types (k = .95), teacher's supervision (k = .99 to 1.00), and child's attentional behavior (k = .77 to .84).

Academic performance score

Child's performance in relation to different lesson contents was evaluated on a scale from 1 (insufficient) to 5 (well to very well) by the teacher (as included in the Teacher Report Form, TRF, (Achenbach, 2001; Verhulst, van der Ende, & Koot, 1997)). Children with ADHD performed less on mathematics (M (SD) = 3.43 (1.23) vs 4.30 (0.79); $p < 0.01$), language arts (3.33 (1.04) vs 4.20 (0.85); $p < 0.001$), sciences (3.46 (1.17) vs 4.44 (0.70); $p < 0.001$), but not on music and arts (3.55 (1.13) vs 3.85 (0.80); ns). As observed classroom attentional behavior may be related to academic underperformance in the ADHD group, an 'overall' performance score (calculated as the average score on mathematics, language, and science) was included as a covariate in further analyses.

Statistical Analyses

To investigate the impact of ADHD and class context on attentional behavior, generalized estimation equation (GEE) models with an exchangeable working correlation matrix were used. GEE is an appropriate technique to take account of the correlations among repeated observations of the same participant without the covariance structure being of central interest (Zeger & Liang, 1986). As the dependent variables, we used two continuous scores: (i) the proportion of time on-task, and (ii) the duration of each on-task interval (attention span). In a first set of analyses, predictors were class group structure (whole group vs small group vs individual work), group (ADHD vs control), and the group x class context condition interaction term. To interpret clinical relevance of these effects, the standardized mean difference between groups was additionally calculated (Cohen's delta or $d = M_1 - M_2 / SD_{pooled}$). This effect size is independent of sample size and defined as small (0.2), moderate (0.5), and large (0.8). In a second set of analyses, the analyses above were repeated with academic content (highly academic vs academic vs non-academic vs

instructional transitions) as the   context condition. In these two sets of analyses, we additionally controlled for academic performance.

To investigate whether the impact of ADHD and class context on attentional behavior is related to levels of teacher supervision, the two main sets of analyses were repeated with additional inclusion of supervision as a covariate. To better understand this relation, we explored: (a) the impact of ADHD and class context on teacher supervision by repeating the main analyses with teacher supervision as the dependent variable; and (b) the effect of teacher supervision and ADHD on attentional behavior by doing analyses with attention variables as the dependent variables and group, teacher supervision, and the interaction term as the predictors. All analyses were performed in SPSS (version 19).

Results

Class Context Characteristics

On average, the group as whole spent 42% (SD 29.2%) of their time on highly academic tasks, 19.1% (SD 29.5%) on less academic tasks, 24.6% (22.7%) on non-academic tasks, and 14.3% (SD 8.6%) on instructional transitions between lessons. During these tasks, 59.5% (SD 26.2%) considered whole group teaching, 6.0% (SD 15.4%) small group work, and 34.5% (SD 27.0%) individual work.

Effect of Class Context on   Classroom Attentional Behavior in ADHD and non-ADHD pupils

Table 1 summarizes the main findings of the GEE analyses. Figure 1 shows mean values of attention variables as a function of group and class context conditions.

Table 1

Wald Statistics of GEE Analyses for Group and Class Group Structure/Academic Content Type with Respect to Attentional Behavior Variables

	Group[a]	Context[b,c]	Group x Context
Class group structure[b]			
Time on-task	12.23***	18.36***	6.87*
Attention span	4.04*	1.90	0.42
Academic content[c]			
Time on-task	22.82***	12.26**	0.21
Attention span	19.37***	34.30***	8.18*

Note. [a]Group (ADHD vs control); [b]Class group structure (whole class group vs small class group vs individual work); [c]Academic content (highly academic vs less academic vs non-academic vs instructional transition)

***p < 0.001; **p < 0.01; *p < 0.05

Class structure and classroom attentional behavior: There was a main effect of group: Children with ADHD displayed less time on-task and shorter attention span than controls. With respect to on-task, there was a main effect of class structure with greater time on-task during small group work compared to individual work *(p < 0.001)*. There was also an interaction between ADHD group x class group structure for time on-task: Children with ADHD were significantly less on-task than controls during individual work *(M$_{diff}$ = 8.25%; CI: 2.27 - 14.22; p < 0.001)* and whole class group teaching *(M$_{diff}$ = 10.24%; CI: 5.97 - 14.52; p < 0.001)*, but not during small group work *(M$_{diff}$ = 2.40%; CI: -3.05 - 7.86; ns)*. Though the interaction effect was not significant for attention span, the smaller effect size between groups during small group work as compared to whole group work and individual work suggest that similar effects as those for on task may be present. Effect sizes (Cohen d) are included in Figure 1.

Figure 1. Group differences (ADHD vs control) in mean values (with 95% CI) of time on-task *(left)* and attention span *(right)* across different class groups structures *(top)* and academic content types *(bottom)*. Standardized group differences in each class condition are presented as Cohen d.
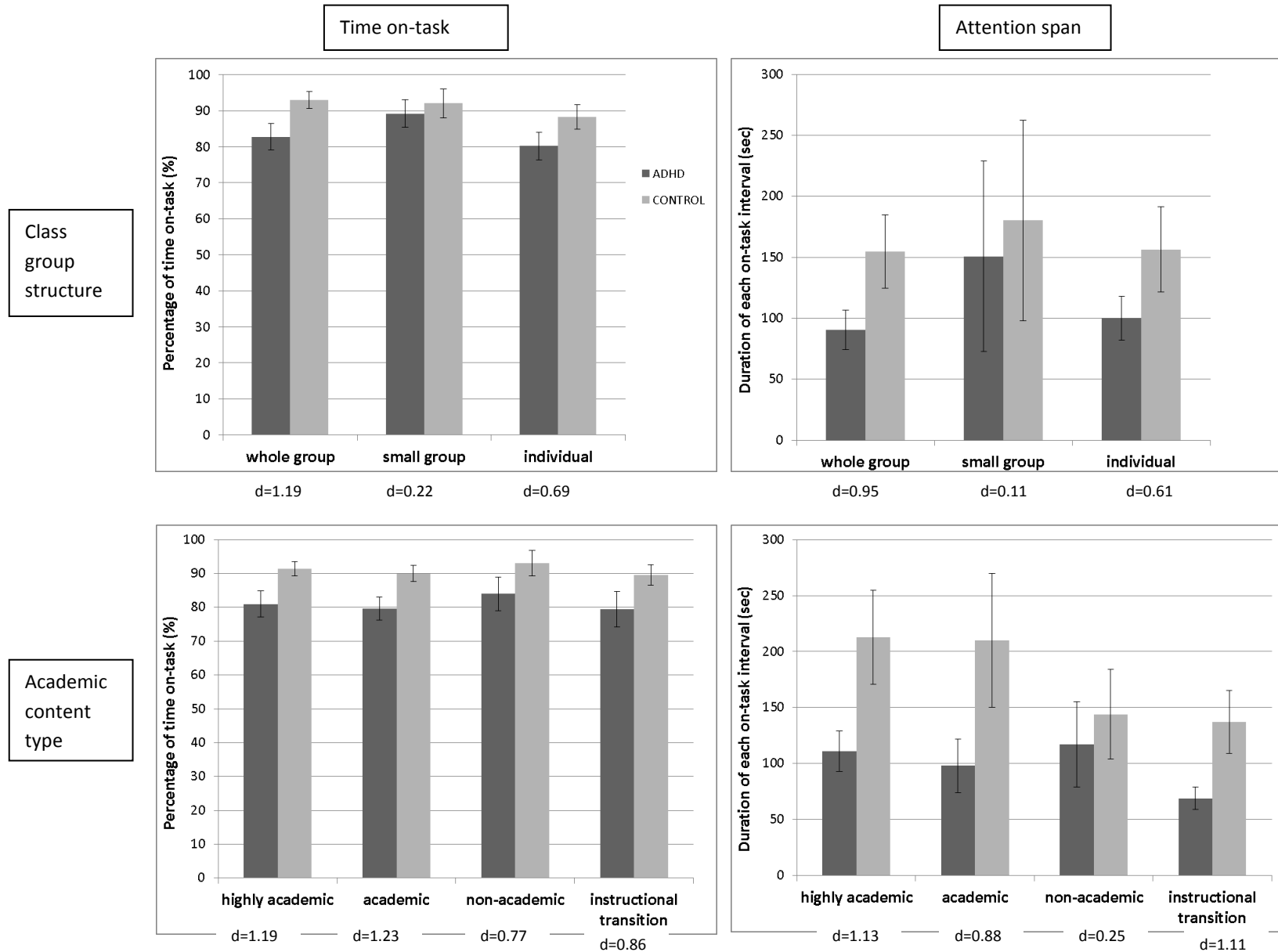
Academic content and classroom attentional behavior: There was a main effect of academic content type with higher on-task levels during music and arts lessons compared with science lessons *(p < 0.01),* mathematics/language *(p < 0.01),* and instructional transitions *(p < 0.01)*. Longer attention span was noted during both mathematic/language *(p < 0.01)* and sciences *(p < 0.05)* as compared to transitions. The interaction between ADHD group and academic content was significant for attention span: The ADHD group had significantly shorter attention span than controls during mathematics/language lessons *(M_{diff} = 102 sec; CI: 57 – 148; p < 0.001),* sciences *(M_{diff} = 112 sec; CI: 49 – 175; p < 0.001)*, and transitions *(M_{diff} = 68 sec; CI: 37 – 98; p < 0.001),* but not during music/arts *(M_{diff} = 27 sec; CI: -27 – 81; ns)*. Though the interaction effect was not significant for time on-task, larger effect sizes in the more academic settings as compared to the non-academic setting suggest that similar effects as those for attention span may be present. Effect sizes (Cohen d) are included in Figure 1.

Influence of academic performance: Teachers reported that academic performance of children with ADHD was significantly lower on mathematics, language arts, and sciences (but not on music and arts) (see partcipants' description). The overall performance score was weakly correlated with time on-task (Pearson r = .17) and attention span (r = .12). When this score was included as a covariate in the models described above, academic performance did no longer contribute to variations in attention variables and did not alter the relations described above.

Effects of Teacher Supervision on the relation between context and attentional behavior in ADHD and non-ADHD pupils

As the teacher may play an important role in adapting environmental demands to the child's specific needs, individual levels of teacher supervision may mediate the relation between context and attention in children with and without ADHD. Therefore, the amount of supervision was included as a covariate in previous analyses (described under c; see Table 2). The rationale for this analysis was based on findings with regard to: (a) the amount of teacher supervision varied as a function of group and class context; and (b) the level of teacher supervision varied in relation to attentional behavior.

(a) *Effect of class context and group on teacher supervision:* There was a main effect of group on levels of teacher supervision *(Wald χ^2 = 5.81; p < 0.01 in the model with classgroup structure; and Wald χ^2 = 17.56; p < 0.001 in the model with academic content)*: Children with ADHD received more individual teacher guidance than their control classmates across all settings *(M(SE) = 7.1(0.7)% vs 4.3(0.9)%)*. There was a main effect of class group structure *(Wald χ^2 = 21.57; p < 0.001)*: Teacher supervision was greater during small group work compared to whole class group teaching *(M(SE) = 8.4(1.8)% vs 3.7(0.3)%; p < 0.05)*. There was also a main effect of academic content *(Wald χ^2 = 37.26; p < 0.001)*: Teacher supervision was higher during mathematics/language lessons than during music/arts lessons *(M(SE) = 5.0(0.4)% vs 3.4(0.5)%; p < 0.05)*. With respect to transition periods, teacher supervision was lower as compared to mathematics/language *(M(SE) = 2.5(0.2)% vs 5.0(0.4)%; p < 0.01)* and sciences *(M(SE) = 2.5(0.2)% vs 4.7(0.6)%; p < 0.05)*. The interaction effects of ADHD group x class group structure *(Wald χ^2 = 2.67; ns)* and ADHD group x academic content type *(Wald χ^2 = 3.41; ns)* were not significant.

(b) *Effect of teacher supervision on classroom attention:* Higher supervision levels significantly predicted longer attention span *(Wald χ^2 = 8.73; p < 0.01)*, but not higher levels of time on-task *(Wald χ^2 = 0.21; ns)*. This relation was similar for ADHD and control group *(on-task level: Wald χ^2 = 0.14; ns; attention span: Wald χ^2 = 2.95; ns)*.

(c) *The effect of teacher supervision on the relation between context x group and attention:* We investigated the impact of group and class context on attention when the overall amount of individual teacher supervision was controlled. When included in these models, teacher supervision did no longer contribute to attentional behavior and did not alter main findings with regard to the impact of ADHD group x class context conditions (see Table 2).

Table 2

Wald Statistics of GEE Analyses for Group and Class Group Structure/Academic Content Type Controlling for Teacher Supervision with Respect to Attentional Behavior Variables

	Group[a]	Context[b,c]	Group x context	Supervision
Class Group structure[b]				
Time on-task	16.91***	18.93***	9.13**	2.81
Attention span	4.75*	1.77	0.43	2.29
Academic content[c]				
Time on-task	29.02***	12.39*	0.22	0.99
Attention span	25.01***	33.89***	8.29*	0.95

Note. [a]Group (ADHD vs control); [b]Class group structure (whole class group vs small class group vs individual work); [c]Academic content (highly academic vs less academic vs non-academic vs instructional transition)

***p < 0.001; **p < 0.01; *p < 0.05

Discussion

This study investigated the influence of different instructional class contexts on attentional behavior (operationalized as percentage of time on-task and attention span) among children with and without ADHD within their naturalistic classroom environment. Firstly, effects of different class group structures and academic content types on attentional behavior in ADHD and non-ADHD groups were investigated. Secondly, the impact of concurrent levels individual teacher supervision across these conditions was examined and its effects on attentional behaviors were explored.

Related to the first research aim, this study supported a differential influence of class context on attentional behavior in children with and without ADHD. This despite the fact that children with ADHD *overall* showed less time on-task as compared to controls and the fact that instructional conditions have an impact on attentional behavior in *all* children. The finding that children with ADHD generally displayed lower on-task levels compared to their

peers is consistent with previous results in naturalistic classroom environments (Abikoff et al., 2002; Junod et al., 2006; Lauth et al., 2006). The classroom is a context with high educational demands in which self-regulatory (Barkley, 1997) and motivational (Sonuga-Barke, 2005) problems could exacerbate off-task and disruptive classroom behavior (e.g., hyperactivity, aggressive behavior) in children with ADHD. In line with Rapport et al. (2009), we also found shorter attention span (and relatedly, attention shifts) in children with ADHD. They suggested that such attention processing deficits are consistent with theoretical models of ADHD predicting attentional resource problems (Sergeant, 2000) and working memory deficits (Rapport et al., 2008). Lower levels of attention were significantly related to academic underperformance, which was obviously more present in the ADHD sample.

In both groups, attentional behavior varied as a function of instructional settings: there was a beneficial effect of small group work in terms of on-task levels as compared to individual work. This is likely to be due to the fact that small group work provides high levels of structure, more active roles for children, and high opportunities for individual teacher feedback (Baker et al., 2008; Downer, Rimm-Kaufman, & Pianta, 2007); a finding supported in the current study. Though whole group teaching is associated with a high level of teacher-initiated structure, it provides only little opportunities for individual teacher-child interactions, whereas the opposite is considered to be true for individual work (Baker et al., 2008). Our results differ however from those in other studies that reported higher off-task behavior during teacher-initiated class activities (whole class group teaching) versus choice of self-pacing and determination (individual and small group work) (Lauth et al., 2006; Zentall, 1980). This discrepancy with respect to individual work could be due to different operationalisations of categories across studies. In our study, children could sometimes 'choose' to complete an individual assignment, but most of the time they could not 'choose' their specific activity. Individual work included, for example, highly academic exercises for which high self-regulatory and motivational skills are needed to complete such tasks. We also found that attentional behavior varied as a function of academic content of sessions. In all children, non-academic tasks such as music/arts lessons were associated with higher time on-task as compared to other academic content categories (i.e., maths/language, sciences, and instructional transition periods). During academic lessons, attention span was longer as compared to transition periods. It may simply be the case that the task demands of

transitions call for more switches between tasks, or create more wait states in which an operationally defined break in attention is just complying with task demands. Alternatively, this could be due to the fact that during these academic tasks (maths/language) but not during transitions, teachers' supervision was more intense compared to non-academic ones (music/arts) in an attempt to encourage attention during high demanding tasks; but even in those settings quantity of these interactions was limited.

Most importantly, however, we found a differential influence of context on children with ADHD. Although children with ADHD overall showed less time on-task as compared to controls, this effect was due to group differences during individual work and whole class group teaching, but not during small group work. Though small group work yielded the highest levels of on-task focus in all children, it seems that children with ADHD benefit especially from this specific class group structure even where no additional supervision is given. During small group work, cooperative learning by interaction with peers is considered to be greater than in other settings. Though each of the group structures considered potentially plays a vital role in the learning process (Baker et al., 2008), the amount of small group work is limited during the observation period. One implication of the current study would be the promotion of this sort of class setting for ADHD pupils. Academic content was also important in this regard. Even after controlling for academic performance, shorter attention span in children with ADHD as compared to controls were present during maths/language, sciences, and instructional transition periods, but not during music/arts. Rapport et al. (2009) suggested that, compared to laboratory tasks, classroom academic tasks typically involve more controlled processing, place greater demands on cognitive resources, including the ability to store and manipulate information in working memory, and require complex strategic mechanisms of self-regulation and planning which can adapt flexibly to changes in the classroom environment. As attentional behavior can be seen by the product of child by environment, this result may reflect the outcome of a unique combination of high educational demands of the environment and typical deficits associated with ADHD to cope with these demands.

Related to the second aim, this study investigated whether the interaction between group and context was modulated by teacher's supervision levels. In line with Greene et al. (2002) we found that, in general, teachers provided more supervision for children with

ADHD compared to their normally developing peers. The presence of an adult supervisor has previously been reported to decrease distractibility in children with ADHD (Power, 1992). In our study, higher teacher supervision was significantly related to better attention (increase of attention span) in general: these effects were similar for ADHD and controls across settings. Furthermore even when levels of teacher supervision were taken into account children with ADHD showed less attention. This suggests that -while supportive teacher behavior represents a prime target for intervention- ways to improve the impact of teacher supervision, perhaps by increasing the amount of supervision, need to be considered. Given their high needs for encouragement and reward seen in prior studies (Luman, Tripp, & Scheres, 2010; Sonuga-Barke, 2003), it may be that children with ADHD need a qualitatively different sort of supervisory support to other children (Baker, 2006). It is of course also possible that the normal classroom is not the ideal setting for pupils with ADHD and that special educational settings -where different teaching approaches are used- might be more appropriate.

Despite the fact that keeping attention during academic tasks was more difficult in the ADHD group, teachers did not further increase their individual supervision during these academic assignments as compared to other settings to –at least partly- approach the specific child's needs. Although increased supervision was related to better attention processing in both groups as mentioned above, the currently observed amount of teacher supervision in children with ADHD (though overall higher as compared to control classmates) might still not be sufficient to increase on-task levels during high demanding tasks as children with ADHD were reported to be less able to benefit from a close teacher relationship (Baker, 2006). As observed individual supervision levels are relatively low during an average school day, we could however assume that an additional increase in supervision in children with ADHD in these specific contexts as compared to less demanding ones (not 'overall') could still have a positive effect. However, such adaptations in teacher behavior may yield practical problems considering the increasing number of pupils in today's regular classrooms. It would be of large interest to explore the impact of different 'qualitative' teacher strategies such as proactive teacher practices (Ervin et al., 1998) and the use of explicit rules with clear consequences for non-compliance (Emmer & Stough, 2001) to increase attention levels in children with ADHD within specific instructional contexts. Next to

teacher supervision, other adaptive classroom management approaches should be considered. For example, this study showed that small group work seems to be a good strategy to increase attention especially in children with ADHD. Additionally, the special structuring of classroom transitions, for example, has been proven to be an effective way of reducing disruption (Lee, 2006).

The study had many strengths. To the best of our knowledge, this was the first study to investigate different measures of attention in children with ADHD and their normal classmates across different instructional contexts; not only class group structure and academic content type (inclusive instructional transition periods) were included, but also individual teacher supervision levels as teachers are supposed to adapt the environment to the child's needs. To capture a larger variety of settings, we observed children in their naturalistic classroom for a longer period of time (two consecutive schooldays). However, there were limitations. First, the naturalistic class environment represents a less-standardized, less-controlled setting as compared to the laboratory context. It was not possible to control for every aspect of stimulation or structure within the environment; for example, the effect of the camera, the presence of the examiner, additional noise, and unexpected interference. As the child with and without ADHD were observed simultaneously in the same classroom, it is reasonable to assume that these effects were similar for both children. Additional analyses supported the observation for longer periods as teacher supervision was found to be significantly higher on day 1 than on day 2 ($p < 0.05$). However, this association did not alter the main findings of this study as results were confirmed for day one and day two separately. No association was found for attentional behavior. Second, despite the ecological nature of our observations, findings may not generalize to all settings and all school days (Hintze & Matthews, 2004). Current findings relate to Flemish regular elementary classrooms and therefore may not be representative for other world parts, special education settings, or home environments. Third, in this study, we included children with ADHD removed from medication to observe the 'true nature' of their behavior. Therefore, unusually high levels of inattattention may be present in at least some students' part. This may limit generalisibility of conclusions to all children with ADHD, particularly when treated with medication. Fourth, we considered the average duration of each on-task interval as a measure for attention span (and relatedly attention shifts). This measure may

however not map exactly on the attention span construct as operationalized when investigating attention processing during controlled taks. Inattentive behavior was studied as a meaningful construct in itself, not as a proxy for neural functioning (for example alerting and orienting processing). Fifth, it is not clear to what extent peer interactions during small group work could have influenced behavior in children with ADHD. As favorable effects of peer tutoring interventions have been described (DuPaul et al., 1998), it would be interesting to further explore the quality of these close cooperations between pupils. Sixth, baseline rates of teacher supervision in the normal class environment were low overall. Therefore, we only assessed supervision quantity (amount), but not quality (positive support, negative feedback) of teacher-child interactions which may be interesting to include in future studies. Additionally, the finding of overall higher levels of supervision in the ADHD group restricted generalization of our findings. To fully explore the effect of teachers' practices on attentional behavior in children with and without ADHD within different instructional contexts, a semi-experimental study -in which not only class context conditions but also levels of teacher supervision are similar for both groups- would be helpful. Finally, such an approach could be used to further investigate specific combinations of class group structures and academic content types and their effect on attention. Though we observed children during a longer time period, the occurrence of some conditions (especially small group work) was too small in the naturalistic setting to allow additional subdivisions. Additional analyses however showed that small group work was present during both non-academic tasks (30%) and (highly) academic tasks (70%). The beneficial effect of small group work on attentional behavior could therefore not uniquely be related to the overlap with less-demanding, non-academic tasks.

In sum, this study supported a differential impact of instructional contexts on attentional behavior in children with ADHD as compared to their normal developing classmates. Though children with ADHD were overall less on-task than their peers, group differences were particularly clear during whole group teaching, individual work, and instructional transition periods, and on highly academic tasks. High self-regulation, information-processing, and motivational demands within these contexts interact with the specific deficits associated with ADHD. Teachers did provide more supervision to ADHD pupils but despite this the deficits seen persisted. Alternative strategies such as small group

work may have a stronger impact on attentional behavior, especially in children with ADHD. Further research to properly understand the dynamics of the class environment is needed to determine effective teacher strategies and to guide academic interventions for increasing attention levels which may lead to better academic performance and long-term outcomes in children with ADHD (Daley & Birchwood, 2010).

Acknowledgements

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Part B

ADHD and Circadian Variability

So far, minor attempts have been made to investigate circadian effects on arousal in ADHD. In this part, we first review the available literature in this research area to define current gaps of knowledge. We then perform longer-term evaluations of heart rate and cortisol in order to detect whether time-specific alterations in arousal patterns are present in children with ADHD as compared to their typically developing peers. The presence of such effects could lead to the adjustment of dosing and timing of ADHD medication to optimally treat problematic behaviour considering its fluctuating expression.

4. Altered Circadian Profiles in ADHD:
An Integrative Review

*Lindita Imeraj, Edmund Sonuga-Barke, Inge Antrop,
Herbert Roeyers, Roeljan Wiersema, Sarah Bal, Dirk Deboutte*

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, in chapter 7, 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 primary aim of this paper was 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 (see current chapter). In chapter 7, we additionally *developed 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) arousal 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 chapter 7; section 1.2 and 1.3 for more detailed information), which in turn have been thought to display spontaneous circadian effects across the day (see chapter 7; section 1.1 and 1.4 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).

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.

Table 1

Overview of Original Studies Evaluating Time-of-day Effects in ADHD Behavior

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Antrop et al. (2005)	14 ADHD, Comb (m); 14 NC	6-12	Not confounding: age, sex, class, stimulant medication Confounding: comorbid ODD, CD	Whole day behavioral observation in the naturalistic classroom: out of seat behavior and noisiness	ADHD: stronger increase in hyperactive behavior after playtime in the afternoon compared to NC
Imeraj et al. (2011)	30 ADHD, Comb (24m, 6f); 30 NC	6-11	Not confounding: age, sex, class, comorbid externalizing and internalizing disorders, stimulant medication (stop for at least 72 h)	Actigraphy for 5 consecutive days in naturalistic setting (simultaneous registration of heart rate)	Significant group x time of day effect: during nighttime: ADHD = NC; during daytime ↑ activity in ADHD as compared to NC: afternoon > morning
Licht and Tryon (2009)	9 ADHD Comb (8m, 1f); 9 NC	8-10	Not confounding: age, sex, stimulant medication	Actigraphy for 7 consecutive days in naturalistic setting	Significant group x time of day effect: ADHD has ↓ activity during nighttime, but ↑ activity during daytime compared to NC
Porrino et al. (1983)	12 ADHD, Comb (m); 12 NC	6-12	Not confounding: age, sex, class, stimulant medication Confounding: comorbid CD, LD	Actigraphy for 7 consecutive days in naturalistic setting	Overall activity levels in ADHD > NC, but situational factors (structured academic lessons) increase differences between groups
Tsujii et al. (2007)	16 ADHD, Comb (13m, 3f); 20 NC	7-12	Not confounding: age, sex, stimulant medication (stop for at least 48h) Confounding: comorbid ODD	Actigraphy 7 consecutive days in naturalistic setting	ADHD: ↑ activity during afternoon in-seat classes, but no difference during morning classes or less structured afternoon classes, compared to NC

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Wehmeier et al. (2011)	105 ADHD; 51 placebo vs 54 atomoxetine		Not confounding: age, sex, psychiatric comorbidity, previous stimulant use	Performance test at different times of the day (morning, noon, afternoon/early evening); infra-red motion-tracking device	Both ADHD groups: circadian pattern of performance; no differential treatment effect over 24 hours (sustained efficacy of atomoxetine over 24 hours)
Zagar and Bowers (1983)	43 ADHD, Comb (31m, 12f); no NC	M 10.4, SD 9 m	Not confounding: stimulant medication	Observation of attention and activity Cognitive task for the evaluation of performance	ADHD: ↑ levels of activity and inattention in the afternoon. Cognitive performance better in the morning.

Note. ADHD: attention-deficit hyperactivity disorder; NC: normal control; Comb: combined type; Inat: inattentive type; Hyp: hyperactive-impulsive type; m: males; f: females; ODD: oppositional-deviant disorder; CD: conduct disorder; LD: learning disorder

[a] Variables were considered as not confounding when subjects were matched, or when no differences between groups were reported.

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.

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).

Table 2

Overview of Original Studies Evaluating Sleep-wake Rhythms with Sleep Questionnaires and Actigraphy in ADHD

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Boonstra et al. (2007)	33 ADHD, 32 Comb and 1 Hyp (16 m, 17 f); 39 NC	ADHD: M 37.9, SD 10.3	Not confounding: age, sex, stimulant medication (not medicated) Possibly confounding: comorbid depression and anxiety	Actigraphy for 7 nights (placebo condition prior to participation in medication trial)	Daytime activity: ADHD > NC; nighttime activity: ADHD = NC ADHD: ↑ sleep onset latency, ↓ sleep efficiency, and shorter within-night periods of uninterrupted sleep compared to NC
Chiang et al., 2010	325 ADHD, 174 Comb, 130 Inat, 21 Hyp (265 m, 60f); 257 NC	10-17	Possibly confounding: sex, age, subtype, psychiatric comorbidity, stimulant medication	Psychiatric interview for diagnosis of ADHD, other psychiatric disorders, and sleep problems or disorders	After controlling for confounders: all ADHD subtypes: ↑ insomnia, ↑ daytime napping, difficulty morning awakenings, ↑ sleep duration compared to NC; ↑ circadian rhythm problems in ADHD-Comb and ↑ hypersomnia in ADHD-Inat
Corkum et al. (1999)	79 unmedicated ADHD; 22 medicated ADHD; 35 clinical comparison; 36 NC	6-12	Not confounding: age, sex Confounding: IQ, ADHD subtype, stimulant medication, comorbid LD, ODD, CD, anxiety disorder	Sleep questionnaires	ADHD: ↑ prevalence of dyssomnias related to comorbid ODD and stimulant medication
Corkum et al. (2001)	25 ADHD, 5 Hyp, 6 Inat, 14 comb (20 m, 5 f); 25 NC	7-11	Not confounding: age, sex, comorbid ODD and anxiety Confounding: IQ, ADHD subtype, comorbid CD and depressive disorder	Sleep questionnaire and diary Actigraphy for 7 consecutive nights	Subjective longer sleep duration, ↑ sleep onset, difficulty morning awakenings, ↑ bedtime resistance, but no actigraphic differences in ADHD compared to NC

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Crabtree et al. (2003)	97 ADHD (75 m, 22 f) of whom 16 had actigraphy and 69 PSG evaluation; no NC	3-18	Confounding: age, sex, stimulant medication, comorbid mood and anxiety disorders	Sleep questionnaire Actigraphy for the valuation of sleep during 14 days (+ PSG)	Subjective: ↑ prevalence of sleep complaints (e.g., difficulties initiating and maintaining sleep, snoring, enuresis, restless sleep, daytime sleepiness) Objective: ↑ night-to-night variability, delayed sleep onset
Dagan et al.(1997)	12 ADHD; 12 NC (m)	6-12	Not confounding: sex, comorbid disorders Confounding: age, stimulant medication	Sleep questionnaire Sleep unstructured interview Actigraphy for 3 nights	Subjective: ADHD = NC Objective: ↓ sleep efficiency and ↑ nighttime activity levels in ADHD, but no difference in sleep onset or sleep duration compared to NC
Golan et al. (2004)	34 ADHD (26m, 8f); 32 NC (21 m, 11d)	ADHD: M 12.4, SD 4.6	Not confounding: age, sex, stimulant medication (stop 3 days before assessment) Confounding: BMI	MSTL (+PSG)	ADHD: ↑ daytime sleepiness
Gruber et al. (2000)	38 ADHD, 14 Inat, 4 Hyp, 20 Comb (m); 64 NC (m)	6-14	Not confounding: age, sex, stimulant medication, comorbid ODD/CD	Actigraphy for 5 consecutive nights Sleep logs	ADHD: ↑ night-to-night variability in sleep estimates

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Hvolby et al. (2008)	45ADHD, 64 other psychiatric disorder, 97 NC (total: 153m, 53f)	5-11	Not confounding: stimulant medication Possibly confounding: age, sex Confounding: comorbid ODD, CD, emotional disorders	Actigraphy for at least 5 consecutive nights	ADHD: ↑ sleep onset latency and more irregular sleep pattern than psychiatric control and NC group. No effect of comorbid ODD
Hvolby et al. (2009)	45 ADHD, 64 other psychiatric disorders, 212 NC	5-11	Not confounding: stimulant medication Confounding: age, sex, comorbid disorder ODD, CD, emotional disorders	Sleep questionnaire	ADHD: ↑ sleep onset latency, but no difference regarding numbers of awakenings per night and total sleep time per night. No added effect of comorbid ODD
Lecendreux et al. (2000)	30 ADHD (m); 22 controls with LD	5-10	Not confounding: age, sex, pubertal stage, stimulant therapy, comorbid psychiatric disorders	MSTL	ADHD: ↑ daytime sleepiness
Marcotte et al. (1998)	43 ADHD; 11 LD; 25 ADHD/LD; 86 NC	6-12	Not confounding: age, sex, stimulant medication	Sleep questionnaire	↑ sleep and breathing problems and ↑ sleepiness in ADHD, LD, and ADHD/LD compared to NC, but no differences between clinical groups
Mick et al. (2000)	122 ADHD; 105 NC	12-17	Not confounding: age Possibly confounding: sex Confounding: comorbidity, stimulant medication	Sleep questionnaire	↑ subjective sleep problems in ADHD (e.g. difficulty falling asleep, nighttime awakenings, and difficulty waking up), but frequently accounted for comorbidity and stimulant medication

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
O'Brien et al. (2003a)	44 severe ADHD symptoms; 27 mild ADHD symptoms; 39 NC, all from general population	5-7	Not confounding: comorbid psychiatric symptoms Possibly confounding: age, sex, stimulant medication	Behavioral assessments Sleep questionnaire (+PSG)	ADHD symptoms ~ more nighttime awakenings, difficulty initiating sleep, and daytime sleepiness
O'Brien et al. (2003b)	53 stimulant-medicated ADHD; 34 non-medicated ADHD; 53 NC	5-7	Not confounding: age Confounding: sex, comorbid disorders	Sleep habits questionnaire (+ PSG)	Both medicated and non-medicated children with ADHD: ↑ nightmares, ↑ enuresis, but no significant difference in daytime sleepiness. No significant effect of MPH
Owens et al. (2000)	46 ADHD; 46 NC	5-10	Not confounding: age, sex, stimulant medication (no current use), comorbid depression and anxiety disorder Confounding: comorbid ODD/CD, and LD	Sleep questionnaire	ADHD: ↑ sleep disturbances reported by parents (e.g., ↓ sleep duration, ↑ sleep onset latency, daytime sleepiness) and children (↑ bedtime resistance)
Owens et al. (2009)	80 ADHD; 45 NC	6-14	Not confounding: age, BMI, stimulant medication (no current use) Confounding: sex, ADHD subtype, comorbid ODD	Diary on sleep and daytime behavior Actigraphy for at least 5 consecutive days	Subjective: more daytime sleepiness and difficulty getting up on child-report; difficulty falling asleep and difficulty getting up on parent-report. Objective: shorter actual sleep time, fewer sleep interruptions, but more total interrupted sleep in ADHD

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Paavonen et al. (2009)	280 children from general population (146 f, 134 m) were divided in short, average, and long sleepers (based on sleep questionnaire)	7-8		Actigraph Sleep questionnaire ADHD rating scale	behavioral symptoms of ADHD ~ ↓ sleep duration
Pesonen et al. (2010) ~	general population (145 f, 135 m)	8		Behavioral assessments (Child Behavior Checklist) Actigraph for 7 nights (range: 3-14)	Short sleep duration ~ problems in attentional control and externalizing behaviors; irregularity in sleep duration ~ internalizing problems
Schredl et al. (2007)	120 ADHD (64 f, 56 m) (31 Inat, 87 Comb, 2 Hyp) from whom 61 without comorbidity, current substance abuse, and medication intake; 444 NC	18-62	Possibly confounding: age, sex, subtype, stimulant medication, antidepressants, comorbid depression, anxiety disorder, tic disorder, OCD, substance abuse	Sleep questionnaires	ADHD without comorbidity and without medication intake: ↑ sleep problems (e.g., feeling unrefreshed in the morning); comorbidity and depressive symptoms ~ insomnia. No effect of medication.

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Stein et al. (2002)	32 non-medicated ADHD (m); 35 medicated ADHD ; 77 NC (m)	13-16	Not confounding: sex, age, comorbid sever behavioral problems, internalizing disorders, and drug abuse Confounding: medication, internalizing symptoms	Sleep questionnaire	Severity of sleep disturbance: non-medicated ADHD = NC < medicated ADHD with an added effect of depressive symptoms
Surman et al. (2009)	182 ADHD; 117 NC	18-55	Not confounding: sex Possibly confounding: age, comorbid internalizing disorders, stimulant medication	Sleep questionnaire	ADHD: later bedtimes, ↑ sleep onset latency, difficulty going to bed and waking in the morning, ↑ daytime sleepiness, independent of stimulant therapy and comorbidity
Touchette et al. (2009)	2057 children from the general population	1.5-5		Questionnaire to assess developmental trajectories of nighttime sleep duration and hyperactivity	Hyperactivity ~ nighttime sleep duration
Van der Heijden et al. (2005c)	87 ADHD+SOI, 33 ADHD-SOI	6-12	Not confounding: stimulant medication (naïve) Possibly confounding: age, sex, comorbid ODD, anxiety disorder, affective disorder	Actigraphy for 7 consecutive days DLMO (hourly from 6 PM to 10 PM)	ADHD+SOI: delayed sleep phase and delayed DLMO, compared to ADHD-SOI

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Van Veen et al. (2010)	40 ADHD (21m, 19 f) of whom 31 reported SOI; 38 NC	18-55	Not confounding: age, sex, stimulant medication, melatonin, antidepressants, antipsychotics (free for at least one month) Possibly confounding: ADHD subtype, comorbid depression and anxiety, nicotine	Actigraphy for 7 days Dim light melatonin onset during 1 night at hourly intervals between 9 PM to 1 AM	Both groups of ADHD: ↑ sleep onset latency and ↓ sleep efficiency compared to NC. ADHD+SOI: delayed start and end of their sleep period and a delayed melatonin onset compared with ADHD-SOI and NC.
Wiggs et al. (2005)	71 ADHD (63m, 8f); 23 NC	3-15	Not confounding: age, sex, stimulant medication (non-medicated)	Sleep diary Clinical history Actigraphy for 5 nights	Subjective sleep disturbances (e.g., sleep initiation problems) in ADHD No objective group differences in sleep patterns

Note. Both clinical and general population studies are considered. Medication intervention studies were not included in this table. ADHD: attention-deficit hyperactivity disorder; NC: normal control; Comb: combined type; Inat: inattentive type; Hyp: hyperactive-impulsive type; m: males; f: females; ODD: oppositional-deviant disorder; CD: conduct disorder; LD: learning disorder; MSTL: multiple sleep latency test; PSG: polysomnography; DLMO: dim light melatonin onset; SOI: sleep-onset insomnia.

[a] Variables were considered as not confounding when subjects were matched, or when no differences between groups were reported.

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 are 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.

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.

Table 3

Overview of Original Studies Evaluating Circadian Cortisol Rhythms in Children and Adults with ADHD

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Blomqvist et al. (2007)	18 ADHD, 13 Comb (15 m, 3 f) ; 71 NC (47 m, 24 f)	13	Not confounding: age, glucocorticoïd medication Confounding: stimulant medication, sex, ADHD subtype	Saliva cortisol: collected on a school day: one upon awakening and one 30 min later	ADHD: ↓ cortisol levels 30 min after awakening than NC
Freitag et al. (2009)	123 ADHD; 69 NC	6-12	Not confounding: age Confounding: sex, ADHD subtype stimulant medication, comorbid ODD, CD, anxiety disorder	Saliva cortisol: collected on two consecutive weekend days: immediately after awakening, and 30, 45, and 60 minutes thereafter	Cortisol awakening response: ADHD+ODD < ADHD-ODD/CD = NC
Hastings et al. (2009)	170 ADHD, 59 Inat, 25 Hyp, 86 Comb (m); no NC	6-11	Not confounding: stimulant medication Confounding: ADHD subtype and comorbid disorders	Saliva cortisol: one sample collected within 15min of waking	No association between waking cortisol levels and comorbid diagnoses or problems in children with ADHD
Hatzinger et al. (2007)	102 pre-schoolers from the general population	5		Behavioral emotional assessment Saliva cortisol samples: collected at 0, 10, 20, and 30 min after	Hyperactivity/impulsivity symptoms in boys ~ ↑ HPA axis activity

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
				awakening during one regular weekday	
Hirvikoski et al. (2009)	28 ADHD, 24 Comb, 4 Inat; 28 NC	19-54	Not confounding: age, sex Confounding: comorbid depression and anxiety disorder	Saliva cortisol: collected during a separate weekday: after awakening, 30 min after awakening, between 5 PM and 6 PM, and at bedtime, or, at the latest, at 11 PM	Overall cortisol levels and diurnal cortisol rhythm: ADHD = NC
Imeraj et al. (2011)	31 ADHD (all Comb; 22 with and 11 without ODD); 31 NC	6-12	Not confounding: age, sex, comorbid ODD and internalizing disorders, stimulant medication	Saliva cortisol: collected at five times a day (awakening, 30 min after awakening, noon, 4PM, 8PM) across five consecutive days	Cortisol awakening response: ADHD = NC Diurnal cortisol profiles across the day: significant group x time effect associated with the presence of absence of ODD comorbidity (ADHD: flatter slope with relative morning hypo-arousal and evening hyperarousal; ADHD+ODD: steeper slope with relative morning hyperarousal and evening hypo-arousal)
Kaneko et al. (1993)	30 ADHD (25 m; 5 f); 30 controls with ASS	ADHD: M 8.6 SD 3.3	Not confounding: age, sex, comorbid depressive disorder Possibly confounding: comorbid ODD, stimulant medication	Saliva cortisol: collected at 8 AM, 10 AM, noon, 4 PM, 8 PM, and 10 PM, and an extra morning sample on second day	ADHD: majority had no normal diurnal cortisol rhythm

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Ma et al. (2011)	128 ADHD (44 Inat, 52 Comb, 32 Hyp); 30 NC	6-14 y	Not confounding: age, sex, psychiatric comorbidity, ADHD subtype Possibly confounding: intelligence, stimulant medication	Plasma cortisol (and ACTH) collected at 8 AM	ADHD: ↓ morning cortisol levels than NC Hyp: ↓ morning cortisol levels than Inat and Comb ADHD
Pesonen et al. (2011)	General population (143 m; 129 f)	8		Behavioral assessment (ADHD rating scale and Child Behavior Checklist) Saliva cortisol: collected at awakening, 15 min after awakening, 30 min after awakening, 10:30 AM, noon, 5 PM, bedtime	No association between ADHD symptoms and diurnal cortisol pattern
Schulz et al. (1997)	23 aggressive boys with ADHD; 27 nonaggressive boys with ADHD	7-11	Not confounding: age, sex; IQ, medication (free for at least 4 weeks), comorbid depression or anxiety disorder Confounding: CD	Plasma cortisol: collected at 9:45 AM and 9:55 AM	Cortisol levels: aggressive ADHD = nonaggressive ADHD

Study by	Subjects	Age	Confounding variables[a]	Dependent variables and circumstances of evaluation	Differential group effects
Sondeijker et al. (2007)	1768 children from the general population	10-12		Behavioral questionnaires Saliva cortisol: collected on a normal day, shortly after waking up, half an hour later, and at 8 PM	ADHD problems ~ ↑ cortisol levels at 8PM
Susman et al. (2007)	111 children from the general population	8-13		(CMEP) Saliva cortisol: collected on a nonschool day: immediately after awakening, 20 min postwake time, 40 min postwake time, at noon, at 4 PM, and at bedtime	Attention problems ~ ↓ AM to PM cortisol ratio in boys only
Wang et al. (2011)	50 ADHD; 50 NC	6-12 y	Not confounding : age, sex, psychiatric comorbidity, stimulant medication	Saliva cortisol (and DHEA) was collected at 8 AM	Morning cortisol: ADHD = NC

Note. ADHD: attention-deficit hyperactivity disorder; NC: normal control; Comb: combined type; Inat: inattentive type; Hyp: hyperactive-impulsive type; m: males; f: females; ODD: oppositional-deviant disorder; CD: conduct disorder; LD: learning disorder; CMEP: child morningness-eveningness preference scale

[a] Variables were considered as not confounding when subjects were matched, or when no differences between groups were reported.

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).

3. 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. Although some studies have already attempted to adapt medication dose-release methodology to behavioural needs throughout the day (Chavez et al., 2009; Pelham et al., 2001; Sonuga-Barke et al., 2004; Swanson et al., 2004), treatment response curves across the day are still insufficiently documented (Sonuga-Barke et al., 2008) and systematic methods of assessment of time of day effects for clinical purposes need to be further developed. 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 chapter 7, section 1.3 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).

4. 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 can lead to a working hypothesis that could serve as a framework for further research. In chapter 7, we propose a putative model in which 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. There we review the potential implications of this model for clinical practice and future research.

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5. Diurnal Variations in Arousal:
A Naturalistic Heart Rate Study in Children with ADHD

Lindita Imeraj, Inge Antrop, Herbert Roeyers,
Ellen Deschepper, Sarah Bal, Dirk Deboutte

Abstract

Previous studies suggest an altered circadian regulation of arousal in children with Attention-Deficit Hyperactivity Disorder (ADHD) as measured by activity, circadian preference, and sleep-wake patterns. Although heart rate is an important measure to evaluate arousal profiles, to date it is unknown whether 24-hour heart rate patterns differentiate between children with and without ADHD.

In this study, 24-hour heart rate data were collected in 30 non-medicated children with ADHD (aged 6-11) and 30 sex-, class-, and age-matched normal controls in their naturalistic home and school setting, during five days. Simultaneously, 24-hour activity patterns were registered. Confounding effects of demographic variables (e.g., age, sex, BMI, pubertal stage) and comorbid internalizing and externalizing problems on heart rate levels were additionally assessed.

Longitudinal analysis showed that heart rate levels were overall higher in the ADHD group ($p<0.01$) –with largest effects during afternoon and night-, in a model controlling for age. Other factors did not significantly contribute to variations in heart rate levels. Compared to controls, children with ADHD showed higher activity levels during daytime (especially early afternoon), but not during nighttime ($p<0.05$). Post hoc analyses showed that environmental effects may influence daytime variations.

Findings suggest an autonomic imbalance in children with ADHD as compared to controls, with higher heart rate levels in the ADHD group. Nighttime tachycardia in this group could not be explained by nighttime activity levels or comorbid externalizing/internalizing problems. Further research on autonomic functioning in ADHD is recommended because of the major impact of higher resting heart rate on health outcomes.

Keywords: ADHD, arousal, circadian, heart rate, activity

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common child psychiatric diagnoses typified by inattention problems, hyperactivity and impulsivity (American Psychiatry Association, 2000) [4]. Several theoretical models have explained the behavioral symptoms in this developmental disorder in terms of arousal regulation deficits [51, 52, 68]. As arousal is closely related to sleep-wake regulation [50], it is not surprising that arousal is characterized by a circadian rhythm [54]. To date, several research domains have pointed to differential circadian arousal patterns in ADHD. There is evidence that subjects with ADHD show a higher eveningness preference [12, 47, 55], more sleep-wake disturbances [10, 14, 27, 37, 40], and more hyperactivity problems in the afternoon [3, 44, 60, 67]. As findings on this research topic are inconsistent [13, 17, 23, 36], further clarification of time of day effects in arousal is critical to fully understand underlying mechanisms involved in arousal and behavioral symptoms of ADHD.

One of the major systems involved in arousal regulation is the autonomic nervous system [41, 50, 54]. Heart rate has been considered as a reliable, non-invasive measure for the autonomic activity of an individual [35, 49], which is especially related to emotional and motivational aspects of arousal [6, 22, 38]. Heart rate reflects the balance between the activity of the two branches of the autonomic nervous system, the sympathetic and parasympathetic division [38], which are associated with stress and rest states respectively [20, 29]. This parasympathetic branch, more specifically the ventral vagal complex, is also involved in emotion and behavior regulation processes such as attention, motor activity, emotion, and social engagement [42, 43].

To date however it is unknown whether circadian regulation of the autonomic nervous system is different in children with ADHD as no evaluation of 24-hour heart rate patterns is available. One study with a shorter-term evaluation (three periods of 5 min) suggested that children with ADHD have elevated heart rate levels compared to controls [59]. This finding was associated with changes in 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.

The main aim of this paper is to investigate whether 24-hour heart rate patterns under natural environmental conditions are different in non-medicated children with ADHD as compared to normal control children. We have a particular interest in resting heart rate, i.e., nighttime levels, as this measure can be used as an indicator of autonomic balance and vagal tone [57]. Based on a short-term evaluation study [59], we expect elevated heart rate levels, i.e., a decreased vagal tone, in children with ADHD as compared to normal controls. In line with previously reported circadian alterations in arousal, we further hypothesize that group differences in heart rate are particularly expressed at specific times of day.

Additionally, we take into account several possible confounders of heart rate levels. First, demographic variables such as age and sex, but also pubertal stage (Tanner) and body mass index (BMI) could influence heart rate levels [5, 64]. In this context, also average use of caffeine and presence of nightmares were questioned. Second, both externalizing problems such as oppositional defiant disorder (ODD) and conduct disorder (CD) and internalizing problems such as anxiety and depression have been related to different autonomic functioning, i.e., lower and higher resting heart rate levels respectively [20, 32, 35, 39]. Third, activity is hypothesized to influence heart rate levels. We simultaneously assess 24-hour activity patterns in order to explore possible confounding effects on heart rate patterns and to guide interpretations on the behavioral level. We suggest a close relation between activity and heart rate levels, and expect higher activity levels in children with ADHD as compared to normal controls, especially during afternoon hours.

Method

Subjects

Thirty children diagnosed with ADHD (24 boys and 6 girls), aged 6-11, were recruited from a child psychiatric outpatient unit. As controls, we selected 30 age- and sex-matched healthy, normally developing children within the same class as the child with ADHD. Control children had no formal psychiatric or medical diagnosis, and were all medication-free. Children with ADHD had a formal diagnosis of ADHD combined type -both inattention and hyperactivity/impulsivity problems- based on a child and adolescent psychiatric evaluation during which also a structured interview was used to assess symptoms of ADHD in

accordance with the Diagnosis and Statistical Manual of Mental Disorders criteria (Diagnostic Interview Schedule for Children for DSM-IV, parent version (PDISC-IV)) [53]. Exclusion criteria included an IQ less than 80 as measured by the Wechsler Intelligence Scale for Children, third edition (WISC-III-R) [66], pervasive developmental disorders, neurological disorders such as epilepsy, chronic medical conditions such as hypertension, diabetes mellitus, and asthma, and any medical treatment (e.g., atomoxetine or psychotropic medications) except for methylphenidate. Twenty-six children with ADHD took methylphenidate (17 short- and 9 long-acting formulation), but all children were free from treatment at least 72 hours prior to participation in the study. None of the participating children used alcohol or nicotine. Current behavioral and emotional problems were screened in both groups using the Child Behavior Checklist (CBCL) [1, 62] and the Teacher Report Form (TRF) [2, 63].

Procedure

This study was approved by the Ethical Committee of Ghent University Hospital, Belgium. Children with ADHD were recruited from the child psychiatric outpatient unit of the University Hospital Ghent (Belgium). After parents of children with ADHD provided written consent, the school and teacher of the child with ADHD were contacted to seek their collaboration in the study. Teachers primarily selected three sex-and age-matched normally developing classmates without formal psychiatric or medical diagnosis. If all parents of the control group provided written consent, one control child was selected randomly to participate in the study.

Observations were carried out in the naturalistic home and school environment of the children during five consecutive days (three school days and two weekend days). To random the order of weekdays and weekend days, 16 paired (ADHD and control classmate) observations were randomly carried out from Tuesday evening until Sunday evening, and 14 paired observations from Friday evening until Wednesday evening. During schooldays, the child with ADHD and its matched control were exposed to similar contextual conditions. School started between 8:20 and 8:45 AM and finished between 3:30 and 4:00 PM, with recess/lunch periods between 10:00 and 10:30 AM, between noon and 1:30 PM, and between 2:30 and 3:00 PM. In general, academic lessons (mathematics, language arts) were

mostly planned in the morning (70 % vs 30 % in the afternoon), whereas non-academic lessons (music and arts) were mostly scheduled in the afternoon (90 % vs 10 % in the morning).

On the start day of the study, all persons involved attended a meeting during which the course of the study was briefly recapitulated. Length, weight, and Tanner pubertal stage of all children were assessed. Parents reported on children's caffeine use and the presence of nightmares. A detailed explanation on activity and heart rate devices was given. Parents were instructed how children should wear the Actiwatch and practiced how to attach the Actiheart and replace monitoring electrodes. Children received a small reward for their participation.

Measures

Demographic variables

Because of their possible influence on heart rate levels, age, sex, Tanner pubertal stage and body BMI were taken into account [5, 64]. Additionally, average caffeine use and the presences of nightmares in all children was questioned.

CBCL/TRF

The CBCL [1, 62] screens for emotional and behavioral problems in children aged 4 to 18. The CBCL was completed by parents, and a parallel version, the TRF [2, 63], was completed by classroom teachers of all children. The CBCL and TRF contain items rated on a 3-point Likert scale yielding three broadband scales: internalizing, externalizing, and total problems. Both questionnaires have good reliability and validity.

The prevalence of comorbid psychiatric problems was high in our sample of children with ADHD. As both externalizing problems (such as ODD and CD) and internalizing problems (such as anxiety and depression) have been related to lower [20, 32, 35, 39] and higher [20, 35] heart rate levels respectively, the possible influence of externalizing and internalizing problems (as measured by the CBCL) on heart rate levels was taken into account.

Actiheart: 24-hour heart rate patterns

Heart rate was measured with the Actiheart (Cambridge Neurotechnology Ltd, Cambridge, UK), a small single-piece device with a combined heart rate and movement sensor, designed to clip on to two standard ECG electrodes (3M Ag/AgCl 2223, Germany), positioned at the level of the third intercostal space [16]. More detailed technical information on this device has been reported by Brage et al. [11].

In this circadian study, the epoch length was set to 1 min to make longer term evaluation possible. Through an interface, the data were loaded into a software program (Actiheart software, version 2.4, Cambridge Neurotechnology Ltd, Cambridge, UK) and cleaned before further analysis so that bathing and swimming periods were excluded from the analysis. For data analysis, heart rate counts were averaged per hour.

Actigraph: 24-hour activity patterns

An actigraph is an acceleration-sensitive, watch-like device typically worn on the non-dominant wrist (Actiwatch, Cambridge Neurotechnology Ltd, Cambridge, United Kingdom). For the purpose of this study, an epoch length of 1 min was set. Each time an actigraph is moved compared to a reference signal a voltage is generated. The number of movements during a 1 min interval is accumulated and saved before resetting the counter to zero, providing a measure of activity frequency (counts per minute). Through an interface, the actigraph data were loaded into a software program (Sleep Analysis, version 7, Cambridge Neurotechnology Ltd, Cambridge, UK) for further analysis. For the purpose of this study, actigraph data were evaluated in terms of absolute intensity by calculating activity counts per hour.

Statistical Analyses

Demographic variables (age, sex, BMI, pubertal stage, caffeine usus, and presence of nightmares) and scores on the CBCL and TRF were compared between ADHD and control group using analysis of variance (ANOVA) or chi-square tests as appropriate.

Mixed model analysis was conducted with SAS PROC MIXED (SAS, version 9.2) to test whether 24-hour heart rate and activity data differed between ADHD and control group. This

method is preferred above repeated measures ANOVA for the study of longitudinal data [9, 24]. Likelihood ratio tests were used to define the best fitting mixed model for heart rate and activity separately. Different plausible covariance-pattern models, namely heterogeneous compound symmetry, heterogeneous autoregressive, and unstructured covariance patterns were fitted, with or without inclusion of random intercept effects for subject and for day of evaluation within subject in the model. Main predictors of heart rate and activity were diagnostic group (ADHD versus control), time of day (24 hourly data points), day of evaluation (day one to five), and weekday versus weekend day. An interaction term was included for group x time of day to detect differential group effects across time. The heart rate model statement was expanded with other possible confounders of heart rate levels. In the first step, demographic variables (age, sex, pubertal stage, BMI, caffeine use, nightmares) were entered. In the second step, comorbid psychiatric problems (internalizing, externalizing) were entered. Predictors that did not significantly contribute to variations in heart rate were stepwise excluded from the model (significance level at 0.10).

In order to interpret effects obtained with the mixed model, several contrast analyses were additionally performed. First, polynomial time-related contrasts (i.e., linear, quadratic, and cubic effects) were defined for time and for group x time effects. Second, groups were contrasted to evaluate differences in heart rate and activity levels at each time point. To help interpret clinical relevance of statistically significant effects, effect sizes (ES) were calculated as the standardized mean difference between groups (Cohen delta or $d = M_1 - M_2$ / SD_{pooled}), which is independent of sample size. ES are defined as small (0.2), moderate (0.5), and large (0.8). Finally, post hoc analyses were performed to address time-to-time (i.e., peak-to-through) changes across ADHD and control individuals during school days, when contextual influences were similar for both groups. ES were calculated as partial eta squared (η_p^2) to take into accounted associations between repeated measurement data ($time_x$ vs $time_{x+1}$). ES are defined as small (0.01), moderate (0.06), and large (0.14). Comparison of the school versus home assessment was used to explore whether time-to-time effects could be related to environmental school influences.

Results

Demographic Variables and Current Emotional and Behavioral Problems

Age, sex, BMI, pubertal stage, caffeine use and presence of nightmares did not differ between groups (see Table 1). Children with ADHD showed higher ratings on all scales of CBCL and TRF –except for somatic complaints- compared to normal controls (see Table 1).

Table 1

Test Statistics of Demographic Variables and Total Problem Ratings on the CBCL and the TRF

	ADHD M (SD) / n (%)	Control M (SD) / n (%)	$F_{(1,59)}$ / $\chi^2_{(1)}$
Age	8.97 (1.50)	8.80 (1.54)	$F_{(1,59)} < 1$, ns
Sex (n)	24 m (80), 6 f (20)	24 m (80), 6 f (20)	$\chi^2_{(1)} < 1$, ns
Pubertal stage			
- Pre-pubertal pubic hair stage (n)	23 m (96), 5 f (83)	24 m (100), 5 f (83)	$\chi^2_{(1)} < 1$, ns
- Pre-pubertal genital stage (n)	24 m (100)	24 m (100)	$\chi^2_{(1)} < 1$, ns
- Pre-pubertal breast stage (n)	5 f (83)	5 f (83)	$\chi^2_{(1)} < 1$, ns
BMI	16.12 (1.54)	15.88 (1.62)	$F_{(1,59)} < 1$, ns
Caffeine usus (n)	10 (33)	11 (37)	$\chi^2_{(1)} < 1$, ns
Presence of nightmares (n)	3 (10)	1 (3)	$\chi^2_{(1)} = 1.41$, ns
CBCL internalizing	62.77 (8.24)	46.23 (9.25)	53.48***
CBCL externalizing	66.63 (7.70)	44.67 (8.52)	109.74***
CBCL total	68.90 (6.40)	42.60 (9.54)	156.82***
TRF internalizing	52.80 (6.62)	46.10 (6.31)	16.12***
TRF externalizing	58.87 (9.10)	46.20 (5.34)	43.21***
TRF total	59.63 (5.96)	42.70 (5.90)	122.33***

Note. ADHD = attention-deficit hyperactivity disorder; M = mean; SD = standard deviation; n = number in sample; % = percentage of sample; m = males; f = females; BMI = body mass index; CBCL = child behavior checklist; TRF = teacher report form
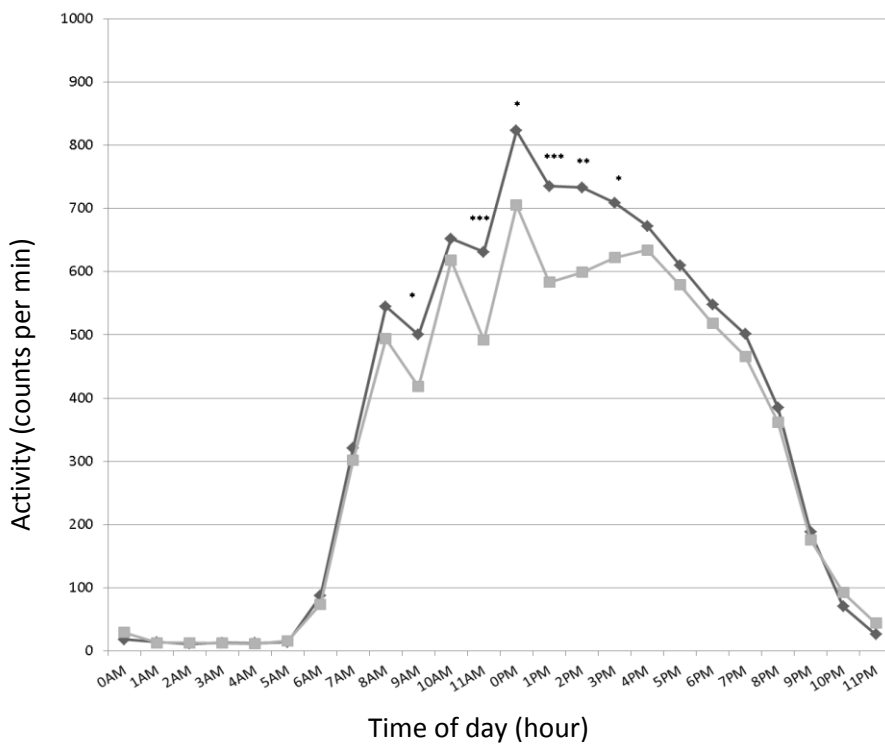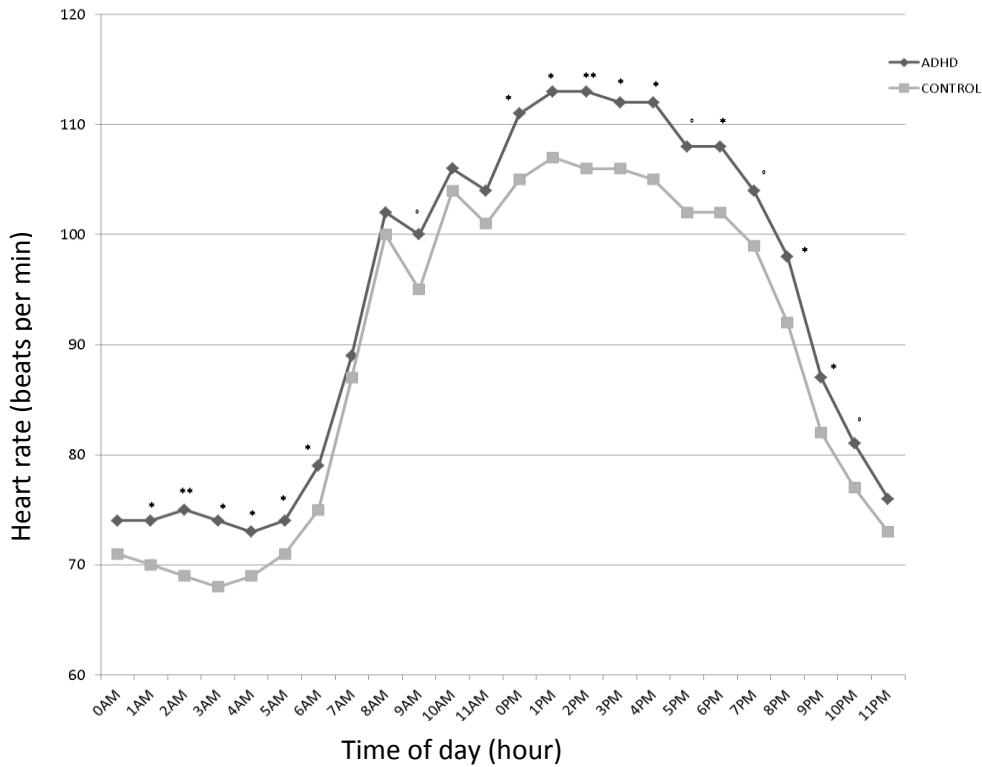
***$p < 0.001$

24-hour Heart Rate Patterns

Considering heart rate, a model with an unstructured covariance pattern including a random intercept for subject fitted best the data. This model revealed a significant effect of diagnostic group ($F(1,7030) = 7.81$; $p < 0.01$), time of day ($F(23,7030) = 135.54$; $p < 0.0001$), but no effect of diagnostic group x time of day ($F(23,7030) < 1$; ns), in a model controlling for day of evaluation ($F(4,7030) = 2.61$; $p < 0.05$), weekday versus weekend day ($F(1,7030) < 1$; ns), and age ($F(1,7030) = 11.40$; $p < 0.001$). Sex, BMI, pubertal stage, caffeine use, presence of nightmares, and comorbid externalizing and internalizing problems were excluded from the final model as these factors did not significantly contribute to variations in heart rate levels.

Polynomial contrasts of the time effect showed a large significant quadratic effect ($t(7030) = -43.36$; $p < 0.001$), next to (smaller) significant linear ($t(7030) = 17.45$; $p < 0.001$) and cubic ($t(7030) = -18.43$; $p < 0.001$) effects. These effects were reflected in the solutions of fixed effects; heart rate levels were significantly higher during daytime than during nighttime in both groups, with an increase in heart rate levels from early morning to noon (steep from 6 AM to 8 AM and more gradual to noon) and a gradual decrease from noon to evening and night.

Overall, heart rate levels were significantly higher in the ADHD group compared to the normal control group. However, polynomial contrasts of the group x time effect showed a significant cubic effect ($t(7030) = 2.33$; $p < 0.05$), reflecting that group differences were particularly expressed at specific times of the day. Contrast analyses confirmed that children with ADHD showed higher heart rate levels as compared to controls, but that these effects were larger during nighttime and afternoon (moderate ES) than during morning hours (small ES) (see Table 2). A visual representation of group differences in heart rate levels, averaged across 5 days, is presented in Figure 1.

Figure 1. 24-hour heart rate (top) and activity (bottom) pattern in children with ADHD and controls, averaged over five days.

Note. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, °$p < 0.10$

24-hour Activity Patterns

Considering activity, a model with a heterogeneous autoregressive symmetry pattern and a random intercept for subject and for day within subject effect fitted the data best. This model showed a significant effect of diagnostic group ($F(1,6854) = 4.33$; $p < 0.05$), time of day ($F(23,6854) = 148.23$; $p < 0.0001$) and a significant interaction effect of diagnostic group x time of day ($F(23,6854)$; $p < 0.05$), in a model controlling for day of evaluation ($F(4,235) < 1$; ns) and weekday versus weekend days ($F(1,6854) < 1$; ns).

Polynomial contrasts of the time effect showed a large significant quadratic effect ($t(6854) = -45.88$; $p < 0.001$), next to (smaller) significant linear ($t(6854) = 12.66$; $p < 0.001$) and cubic ($t(6854) = -11.91$; $p < 0.001$) effects. These effects were reflected in the solutions of fixed effects; activity levels were significantly lower during night than during day hours in both groups, with an increase in activity levels from early morning to noon and a decrease from noon to nighttime levels.

Polynomial contrasts of the group x time effect showed a significant quadratic effect ($t(6854) = 2.83$; $p < 0.01$), reflecting group differences at specific times of the day, but not during others. During day hours, more specifically between 8 and 9 AM and between 11 AM and 4 PM, activity levels were significantly higher in the ADHD compared to the normal control group, but no group differences were observed during evening and night hours. Contrast analyses confirmed moderate to large group effects between 11 AM and 4 PM, small to moderate effects in the morning, but no evidence for group differences during evening and night (see Table 2). A visual representation of group differences in activity levels, averaged across 5 days, is presented in Figure 1.

Table 2

Mean Difference, Pooled Standard Deviation, and Effect Size (Cohen d) for ADHD and Control Group at Each Time Point, Averaged across All Days

	Heart rate			Activity		
	M_{diff}	SD_{pooled}	ES (weekdays/weekend days)	M_{diff}	SD_{pooled}	ES (weekdays/weekend days)
0 AM	3.45	8.15	0.42 (0.73**/0.25)	10.56	72.42	0.15 (0.17/0.18)
1 AM	4.10	7.48	0.55* (0.60*/0.79**)	0.34	137.19	0.003 (0.009/0.004)
2 AM	6.30	9.32	0.68** (0.69**/0.70**)	1.76	137.19	0.01 (0.05/0.02)
3 AM	5.48	8.35	0.66* (0.73**/0.70**)	0.43	137.19	0.003 (0.05/0.002)
4 AM	4.35	7.33	0.59* (0.63*/0.86***)	0.75	137.19	0.005 (0.15/0.004)
5 AM	3.92	7.17	0.55* (0.67**/0.74**)	1.88	137.19	0.01 (0.11/0.006)
6 AM	4.14	7.55	0.55* (0.54*/0.73**)	12.11	72.26	0.17 (0.17/0.04)
7 AM	2.55	8.61	0.30 (0.40/0.28)	19.01	115.35	0.16 (0.27/0.008)
8 AM	1.95	9.99	0.20 (0.13/0.30)	50.85	146.33	0.35 (0.45°/0.12)
9 AM	4.51	9.83	0.46° (0.56*/0.24)	82.69	150.02	0.55* (0.67**/0.15)
10 AM	1.76	10.39	0.17 (0.12/0.15)	34.05	153.20	0.22 (0.10/0.23)
11 AM	3.18	10.35	0.31 (0.22/0.26)	139.42	137.80	1.01*** (0.82**/0.56*)
0 PM	6.20	10.60	0.59* (0.32/0.77**)	118.26	201.95	0.59* (0.45°/0.46°)
1 PM	6.39	10.63	0.60* (0.53*/0.57*)	152.79	177.00	0.86*** (0.52*/0.80**)
2 PM	7.20	10.50	0.69** (0.31/0.88***)	133.63	160.94	0.83** (0.52*/0.71**)
3 PM	6.86	10.56	0.65* (0.43°/0.73**)	87.66	170.69	0.51* (0.40/0.35)
4 PM	7.01	11.90	0.59* (0.19/0.80**)	37.42	200.72	0.19 (0.16/0.45°)
5 PM	5.26	10.44	0.50° (0.36/0.50*)	31.16	183.07	0.17 (0.04/0.30)
6 PM	5.57	10.90	0.51* (0.49°/0.37)	29.84	183.06	0.16 (0.12/0.12)
7 PM	5.08	10.40	0.49° (0.66**/0.30)	34.61	149.66	0.23 (0.39/0.02)
8 PM	5.31	10.48	0.51* (1.01***/0.23)	23.12	132.61	0.17 (0.10/0.16)
9 PM	5.36	9.34	0.57* (1.04***/0.35)	12.33	117.20	0.11 (0.20/0.02)
10 PM	3.83	9.00	0.43° (0.83**/0.19)	21.07	102.27	0.21 (0.17/0.31)
11 PM	3.49	8.28	0.42 (0.81**/0.25)	17.83	84.78	0.21 (0.40/0.23)

Note. M_{diff} = mean difference between groups; SD_{pooled} = pooled standard deviation; ES = effect size (Cohen d)
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; °$p < 0.10$

Possible Contextual Influence on Diurnal Variations in Activity and Heart rate

Mixed model analyses described above did not reveal evidence for significant different effects of weekday and weekend days on activity and heart rate variations. This was confirmed by analyses for weekday and weekend days separately yielding results comparable to our pervious findings (polynomial effects for group x time: heart rate (weekday: $p < 0.05$; weekend day: $p < 0.05$) and activity (weekday: $p < 0.01$; weekend day: $p < 0.01$)). A visual representation of group differences in heart rate and activity levels, averaged across weekdays and weekend days separately, is presented in Figure 2.

However, variations in ES comparing groups at each time point across weekday and weekend days suggest that more subtle weekday/weekend effects may be present (see Table 2); for example, large group effects at 9 AM on weekdays but not on weekend days. Compared to the overall large time of day effect, small effects produced by school schedules (i.e., classroom and playground transitions) may be superimposed on the overall activity and heart rate pattern of children with and without ADHD. Therefore, contrast analyses were performed to estimate effect size of the peak-to-through differences during school hours (i.e., between 8 AM and 4 PM) in both groups (see Table 3). In general, subsequent time-to-time changes in activity were very large between 8 AM and 1 PM for both groups. Only for 10 to 11 AM, children with ADHD showed no significant drop in activity levels in their transition from playtime to class condition. Time-to-time changes in heart rate reflect similar patterns as described for activity except for the noon to 1 PM change. Similar analyses for weekend days could not reveal these large time-to-time changes in the morning (see Table 3). In the afternoon, both groups showed smaller time-to-time variations in activity and heart rate during weekdays and weekend days.

Figure 2. 24-hour heart rate (top) and activity (bottom) pattern in children with ADHD and controls, averaged over weekdays (left) and weekend days (right).
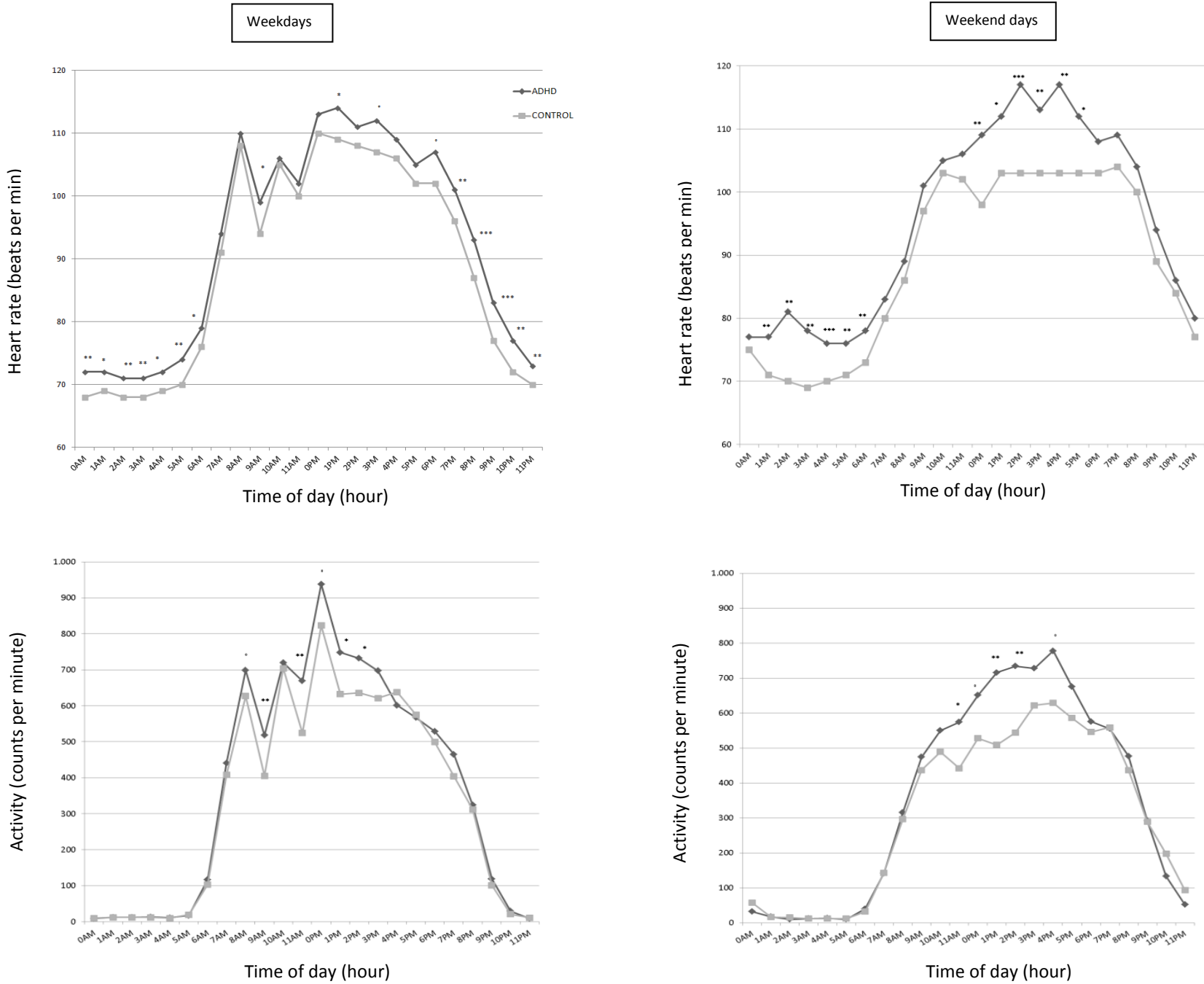
Table 3

Effect Size (η_p^2) of Time-to-time Activity and Heart Rate Variations in Children with ADHD and Controls between 8AM and 4PM during School days and Weekend Days

	School days				Weekend days			
	ADHD activity	Control activity	ADHD heart rate	Control heart rate	ADHD activity	Control activity	ADHD heart rate	Control heart rate
8 AM – 9 AM	0.31**	0.43***	0.62***	0.61***	0.53***	0.28**	0.57***	0.45***
9 AM – 10 AM	0.41***	0.55***	0.52***	0.62***	0.11°	0.04	0.15*	0.18*
10 AM – 11 AM	0.05	0.41***	0.20*	0.40***	0.004	0.02	0	0.01
11 AM – 0 PM	0.46***	0.56***	0.59***	0.59***	0.16	0.11°	0.04	0.004
0 PM – 1 PM	0.31**	0.24**	0.01	0.09	0.007	0.01	0.35**	0.09
1 PM – 2 PM	0.007	0	0.14	0.02	0.001	0.03	0.09	0.009
2 PM – 3 PM	0.03	0.006	0.03	0.03	0.003	0.09	0.01	0.06
3 PM – 4 PM	0.16*	0.004	0.15*	0.01	0.007	0	0.03	0.02

Note. ADHD = attention-deficit hyperactivity disorder

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; °$p < 0.10$

Discussion

To the best of our knowledge this is the first study investigating alterations in diurnal arousal patterns in children with ADHD by 24-hour registration of heart rate combined with activity.

The main aim of this study was to assess whether 24-hour heart rate patterns in non-medicated children with ADHD, registered during five days, under natural environmental conditions, were different as compared to normal controls. Although a typical circadian heart rate pattern with low levels during night and high levels during day hours was revealed [49, 65], we found no significant interaction effect of time of day x group. Heart rate levels in children with ADHD were overall significantly higher than in control children, independent of comorbid internalizing and externalizing problems. However, additional contrast analyses revealed that these group effects were larger at specific times of day, namely afternoon and nighttime hours. Especially the increase in nighttime levels, i.e., resting heart rate, seems important as this measure refers to a lower vagal tone [56, 57]. Our results are in line with Tonhajzerova et al. [59], who found during their short-term evaluation that non-medicated children with ADHD had tachycardia compared to normal controls in both supine position and orthostasis. Their results reflected an autonomic imbalance -low parasympathetic activity and a relative sympathetic dominance-, indicated by low heart rate variability, which the authors hypothesized to be a marker for prefrontal hypo-activity. Thayer and Sternberg [58] described the prefrontal cortex to be part of the central autonomic network (CAN), an entity that controls both visceromotor and behavioral responses that are critical for goal-directed behavior and adaptability. As such they suggested that deficits in the prefrontal cortex may lead to a relative sympathetic dominance as the frontal cortex normally exerts tonic inhibition on brainstem sympathoexcitatory circuits. In ADHD, such a prefrontal hypofunction has been shown with respect to structural and functional neuroimaging, dopaminergic and noradrenergic activity, and neuropsychological executive functioning [8, 25, 26, 61].

Additionally, this study simultaneously registered activity to adjust for locomotor-driven increases in heart rate. Analyses showed a diurnal pattern with low levels during night and high levels during day hours (especially afternoon) in line with previous reports [19, 46].

This diurnal pattern seems to be influenced by environmental conditions and activities. For example, both groups showed a significant peak at 10AM and at 12 AM during school days – but not weekend days- reflecting recess and lunchtime periods. This finding suggests that school-related context factors (i.e., classroom and playground transitions) may be responsible for peak-to-through variations in activity levels, especially in the morning. In the afternoon, activity levels in both groups were higher than at 9 AM and at 11 AM class conditions. Though this could be due to the planning of more academic lessons in the morning and less academic lessons in the afternoon, a similar morning-afternoon effect was observed during weekend days. This finding indicates that morning to afternoon variations in activity are -at least partly- independent of class schedules in children with and without ADHD. However, a significant interaction effect of diagnostic group x time of day was observed. Compared to control children, children with ADHD had higher activity levels during daytime, especially during noon and early afternoon hours, but surprisingly, not during night. Boonstra et al. [10] described a similar pattern in adults with ADHD, i.e., high but stable activity levels during day hours, but no evidence of significant difference at night. Daytime activity levels in children with ADHD may be more variable as differential effects between children with ADHD and control children were described to be particularly expressed when a highly demanding environment and afternoon hours overlap [44, 60]. In the morning, children with ADHD showed no significant drop in activity from the 10 AM playtime to the 11 AM class condition compared to their normal classmates. Such settling-down problems after recess periods in ADHD have previously been described [3]. As this study did not systematically assess environmental factors, it is not sure whether the interaction effect in activity levels refers to a true 'circadian' alteration. Especially the fact that no group difference was observed during nighttime in this study could point towards an important role of environmental conditions to express arousal-related fluctuations in ADHD behavior. In addition, group differences were only detected between 8 AM and 4 PM, indicating the possible involvement of school tasks that were similar for each ADHD and control dyad during this period. Alternatively, it is unlikely that only environmental factors would be responsible for these differences as weekday and weekend days revealed comparable findings considering the expression of ADHD hyperactivity.

In relation to heart rate, we hypothesized that elevated heart rate levels could be driven by higher locomotor activity in the ADHD group. Even though this could be true considering day hours, no such confounding effect of activity on heart rate levels could be retained during night. Nighttime activity levels were not significantly different between groups and could therefore not be responsible for higher nighttime heart rate levels. Although we expected a close relation between heart rate and activity levels, statistically, more 'continue' problems with the inhibition of sympathetic activity did not coincide with the 'specific time of day' problems with the inhibition of behavior. In his polyvagal theory, Porges [42] described two vagal systems: one system associated with the regulation of visceral functions (e.g., heart rate), the other with processes of attention, motor activity, emotion, and social engagement. Although heart rate and activity vary constantly to adapt to changing environmental demands [57], these two systems employ different adaptation strategies [42].

There are a number of issues to consider in evaluating this research as besides activity, also other factors could have elevated heart rate levels in ADHD. First, higher stress levels are expected to elevate heart rate levels so that differential results in ADHD may be due to secondary conditions rather than to ADHD itself. Next to the prefrontal cortex, also limbic structures are part of the CAN and a close association between these regions and baroreflex functions has been described [56]. It has been suggested that anomalies in heart rate could be an early peripheral marker of latent asymptomatic and undiagnosed comorbid emotional disorders which may be the result of accumulated stress [59]. In our study, we looked at confounding effects of psychiatric comorbid problems as physiological dysregulation of the autonomic nervous system has been related to psychiatric disorders other than ADHD [20, 32, 39]. However, we found no evidence that comorbid externalizing and internalizing problems contributed significantly to variations in heart rate levels.

Second, pubertal stage and sex have been reported to influence heart rate levels [5, 64]. Most children in our sample were pre-pubertal without evidence for differences between the ADHD and control group. However, differences for boys and girls in onset of puberty is expected to be about 2 years so that sex differences may be present in our sample but could not be detected due to the small number of girls (n = 6) per group in the study.

Additional analyses of boys only (n = 24 per group) revealed similar results to those obtained for the whole sample.

Third, the confounding effect of stimulant medication must be considered as significant increases in heart rate, especially during the first 6 months of treatment, have been reported [18]. Although all participants were free from medication at least 72 hours prior to participation, to date, it is not sure whether fast-release preparations of methylphenidate could still have influenced cardiovascular functioning. In this study, day-to-day variability in heart rate levels however showed no decrease in the effect pattern from day one to day five. Additional analyses showed that midnight heart rate levels were significantly higher on day 5 than on day one ($p < 0.01$), reducing the possibility that our findings can be explained by longer-term effects of stimulant medication.

Fourth, confounders such as caffeine use and the presence of nightmares may have influenced day- and nighttime heart rate levels. These factors however were not significantly different between groups and did not significantly contribute to heart rate variations. None of the children in our sample used nicotine, alcohol, or illicit drugs.

Finally, regular physical training is known to lower resting heart rate levels. However, we did not systematically assess the amount of sport activities and outdoor play in our sample. Therefore, we cannot exclude the possibility that such activities could have affected heart rate in our control more than in our ADHD group.

In the light of these considerations, our finding of elevated heart rate levels, i.e., hyperarousal, may suggest the necessity to critically re-evaluate the arousal concept in ADHD. Theoretical frameworks [51, 68] have mostly defined ADHD in terms of hypo-arousal deficits -largely ignoring circadian changes in arousal. In our study, we found time of day effects to be important as higher heart rate levels in ADHD were particularly expressed during night and afternoon hours. To our knowledge, nighttime heart rate levels have not been assessed yet in children with ADHD. During daytime periods however, low resting heart rate has consistently been reported in aggressive and antisocial behavior [32, 39]. This finding may not blindly be generalized to ADHD as studies in this population revealed inconsistent results with most of them describing no difference in resting heart rate [28, 30]. Next to possible confounding effects of time of day, these baseline levels may be influenced

by varying levels of anticipatory stress as 'resting' assessments were mostly carried out prior to a laboratory experiment investigating the environmental effects on arousal. Environmental influences may be superimposed on the diurnal pattern as was suggested by more variable effect sizes during daytime in our study. A wealth of studies in subjects with ADHD reported hypo-aroused heart rate responses in relation to for example stress [30] and reward [15, 28]. It is difficult however to compare these findings to those of our study as we did not investigate heart rate in response to such stimuli, under strict laboratory conditions. Nevertheless, we carefully explain our findings in the light of hypo-aroused responsiveness in ADHD. First, it seems that smaller group differences in morning hours may reflect a deviation from the overall higher arousal level, i.e., 'relative hypo-arousal', in children with ADHD during moments of higher academic demands. This effect was however also present throughout weekend days during which cognitive involvement is less plausible. Second, in relation to activity, blunted heart rate responses were reported during peak exercise in ADHD [34]. For a larger min-max difference in activity in children with ADHD (i.e., 812 counts/min for ADHD and 694 for control; $p < 0.01$), our findings reveal a comparable min-max difference in heart rate (i.e., 40 bpm for ADHD and 39 for control; ns), possibly indicating a lower dynamic autonomic potential in children with ADHD than could be expected based on their activity pattern. Alternatively, hyperaroused response patterns have been proposed in ADHD as sustained by higher heart rate levels in response to for example reward [33]. Hyperarousal deficits have additionally been supported by the use of α_2 adrenergic agonists such as clonidine for the effective treatment of ADHD symptoms [48]. These drugs, originally developed for the treatment of hypertension, decrease the firing of noradrenalin neurons in the locus coeruleus, resulting in decreased arousal [7]. A similar action of atomoxetine, a noradrenalin re-uptake inhibitor used to treat ADHD, has been described. Li et al. [31] found an autonomic shift from tachycardia to bradycardia (decrease of sympathetic and increase of parasympathetic tone) after drug administration in rats. This contrasts with the action of methylphenidate, a dopaminergic agent, that is known to increase arousal states in ADHD. Altogether, these findings point to the involvement of time- and context-related aspects in the dynamic modulation of arousal deficits in ADHD, which should be taken into account in future research evaluating deviations from 'optimal' arousal levels (hypo- and hyperarousal) in ADHD.

In summary, we suggest an autonomic imbalance with overall higher heart rate levels – particularly expressed during night and afternoon hours- in our sample of non-medicated children with ADHD. This finding seems independent from activity levels or comorbid psychiatric problems. However, further research is needed to validate our results in a larger sample with heart rate variability as a measure for autonomic function and to assess longer-term effects of these findings in children with ADHD. Higher resting heart rate may have a major impact on health outcomes as an association with higher morbidity and mortality from both cardiovascular and non-cardiovascular diseases has been described [21, 45]. Also the long-term use of psychostimulants must be questioned if overall heart rate levels are 'truly' increased in children with ADHD.

Acknowledgements

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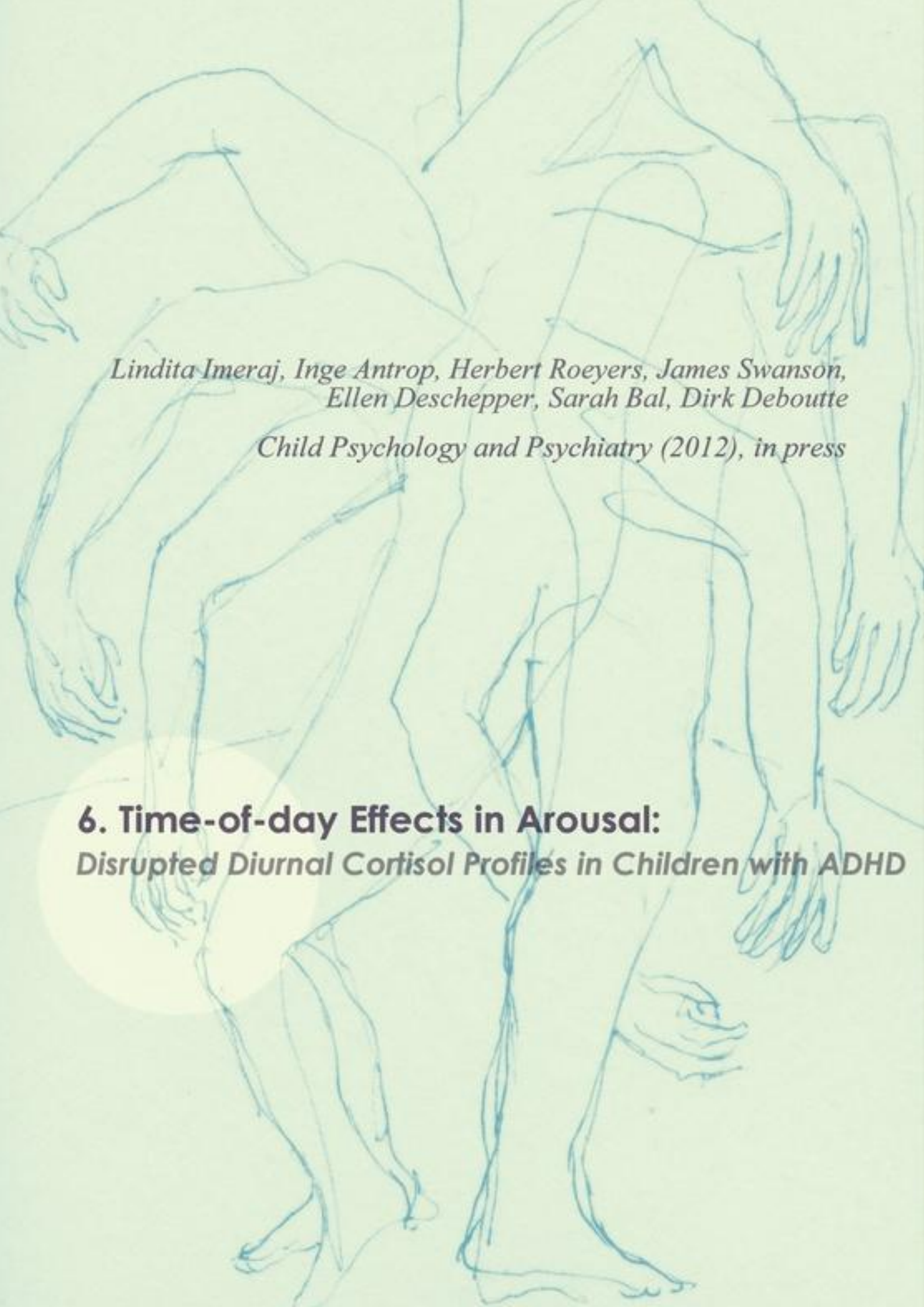
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Lindita Imeraj, Inge Antrop, Herbert Roeyers, James Swanson,
Ellen Deschepper, Sarah Bal, Dirk Deboutte

6. Time-of-day Effects in Arousal:

Disrupted Diurnal Cortisol Profiles in Children with ADHD

Abstract

Background. Fluctuations in attention-deficit hyperactivity disorder (ADHD) symptoms related to regulatory deficits in arousal states are themselves characterized by circadian rhythms. Though cortisol is an important circadian arousal-related marker, studies focusing on across-the-day cortisol variations in ADHD are scarce. There is no study with multiple measurements to take into account interday and intraday variability.

Methods. Salivary cortisol was sampled five times a day (awakening, 30 min after awakening, noon, 4PM, 8PM) across five consecutive days in 33 children with ADHD (22 with and 11 without oppositional defiant disorder; ODD) and 33 class- and sex-matched controls (aged 6-12). The cortisol awakening response (increase from awakening to 30 min after awakening) and the diurnal cortisol profile (across-the-day variations) were compared for ADHD with ODD (ADHD+ODD) and without ODD (ADHD) subgroups and the control group.

Results. The cortisol awakening response was not significantly different between groups. However, longitudinal analyses to evaluate cortisol profiles across the day revealed a significant group x time effect (p<0.001). More specifically, compared to each other, the ADHD subgroup 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 (p<0.001).

Conclusions. Findings support time-related arousal disruptions in children with ADHD associated with the presence or absence of ODD comorbidity. We recommend research on cortisol in larger samples for a better understanding of arousal mechanisms involved in ADHD not only with and without ODD but also with other comorbities which may have implications for timing of arousal-based treatments.

Keywords: ADHD; ODD; circadian; HPA axis; cortisol; arousal

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders in children, characterized by pervasive symptoms of inattention, hyperactivity and impulsivity in home and school settings (Taylor et al., 2004). These behavioural symptoms have been explained by deviations from an optimal arousal level (hypo- or hyperarousal) (Sonuga-Barke et al., 2010). Such deficits in arousal modulation in ADHD have been studied by examining cortisol level in saliva, which is a reliable peripheral measure to evaluate hypothalamic-pituitary-adrenal (HPA) axis functioning (Kirschbaum & Hellhammer, 1989). Cortisol influences regulation of attention, behaviour, and emotion by affecting processes within the prefrontal cortex (PFC) and hippocampus (HC) (Erickson, Drevets, & Schulkin, 2003). Anatomical and functional abnormalities in these brain regions have been observed in ADHD (Himelstein, Newcorn, & Halperin, 2000; Plessen et al., 2006), and altered cortisol concentrations in these regions may be associated with maladaptive control of attentional, behavioural, and emotional processes in ADHD (Hastings et al., 2009).

It is well-established that behavioural symptoms and physiological functions fluctuate across the day (Antrop, Roeyers, & De Baecke, 2005) in circadian rhythms thought to be driven by the suprachiasmatic nucleus (SCN) in the ventral hypothalamus. Arousal is characterized as a physiological and psychological state of being awake, aware and alert that also varies across the day (for a review see: Silver & LeSauter, 2008). Evidence for disrupted circadian regulation of arousal patterns in ADHD has been reported for eveningness preference (Susman et al., 2007), sleep-wake disturbances (Cortese et al., 2009) and excessive daytime sleepiness (Lecendreux et al., 2000), higher heart rate levels particularly expressed during specific times of day (Imeraj et al., 2011), and afternoon hyperactivity problems (Antrop et al., 2005). Results are mixed (Cohen-Zion & Ancoli-Israel, 2004), so further clarification of time-of-day effects in arousal is important. From a theoretical perspective, disrupted circadian arousal-related effects in ADHD (i.e., hypo- and hyperarousal at different times of day) may reflect critical mechanisms underlying behavioural fluctuations in ADHD. From a practical point of view, knowledge of such effects could potentially guide more appropriate timing of diagnostic and research assessments as well as delivery of treatments for ADHD.

Only minor attempts have been made to evaluate time-of-day effects in cortisol levels as a proxy for arousal patterns in ADHD. Variations in cortisol levels in ADHD have been investigated mostly with regard to stress tasks (Hong et al., 2003). Time information reaches the HPA axis through connections between the circadian pacemaker and the paraventricular nucleus of the hypothalamus which contains corticotropin releasing hormone neurons. This circadian input is reflected in a typical diurnal secretion pattern of cortisol -the end product of the HPA axis- with a trough around midnight, a large trend upward toward morning and a peak 30 to 45 min after awakening, called the cortisol awakening response (Haus, 2007).

The available evidence on across-the-day fluctuations in cortisol levels in ADHD points towards distinctive diurnal patterns (Kaneko et al., 1993). However, findings are inconsistent across studies and suggest both hypo- and hyperarousal patterns at different times of day. Blomqvist et al. (2007) reported awakening cortisol level in 13-year old children with ADHD was reported to be lower than in age-matched controls, but Freitag et al. (2009) found the awakening level and the awakening response (change after awakening) to be normal in 6-to-13 year old children with ADHD without comorbid disorders. In the general population, attention problems in 8-13 year old boys have been related to a lower morning-to-afternoon cortisol ratio, but whether this was due to lowered awakening or elevated afternoon cortisol level or both was not specified (Susman et al., 2007). In a subgroup (10-12y), elevated evening levels were found in both boys and girls (Sondeijker et al., 2007), but a study of preschool children reported higher awakening levels (Hatzinger et al., 2007). Some studies have investigated the effects of comorbidity of ADHD with oppositional defiant disorder (ODD), which is the most frequent comorbidity in clinical samples and is associated with poor prognosis. For example, cortisol levels were lower than normal in children with comorbid ADHD and ODD/conduct disorder (CD) (King, Barkley, & Barrett, 1998) and in clinic-referred disruptive boys (McBurnett et al., 2000), but this deficit may be normalized by treatment with stimulant medication (Kariyawasam, Zaw, & Handley, 2002). In some studies of ADHD children, lowered awakening response (Freitag et al., 2009) or lower basal values (Kariyawasam et al., 2002) were associated with comorbid ODD, but this pattern was not confirmed by others (Hastings et al., 2009). Such discrepancies suggest that ADHD with comorbid ODD/CD may differ from ODD and CD and other aggressive behaviour without

ADHD. According to the hypo-arousal theory (Raine, 1996), the latter have typically been linked to both lower basal cortisol levels (McBurnett et al., 2000) and lower morning values (Pajer et al., 2001).

A major limitation of previous research is restricted sampling of cortisol, which is highly variable within individuals and across time of day. Some studies have assessed only awakening cortisol during one (Blomqvist et al., 2007; Hatzinger et al., 2007) or two (Freitag et al., 2009) study days, while others included multiple daytime measurements (Kaneko et al., 1993; Sondeijker et al., 2007; Susman et al., 2007) across a single study day. There is a consensus that intra- and interday variability in cortisol patterns call for full circadian evaluation with multiple time points sampled on a given day across several days (Bartels et al., 2003; Houtveen & de Geus, 2009), but this methodological standard has not been applied in ADHD research.

Cortisol levels were obtained over multiple days (three weekdays and two weekend days) with multiple measurements across each day (two waking and three consecutive samples) in ADHD children compared to age-matched controls. This allows for evaluation of across-the-day fluctuations in cortisol based on average levels of the individual participants. Though some authors reported cortisol awakening response to be a reliable predictor for consecutive daytime levels (Edwards et al., 2001), others questioned this relationship (Oskis et al., 2009). Therefore, we assessed the cortisol awakening response (increase in cortisol levels from awakening to 30 min after awakening), and diurnal profile (variations in cortisol levels across the day). Since the literature suggests that ODD comorbidity may influence these findings, two subgroups were taken into account -ADHD with ODD (ADHD+ODD) and without ODD (ADHD). Based on our hypothesis of disrupted arousal-related circadian rhythm in ADHD (i.e., hypo- and hyperarousal at different times of day), we expected (i) a significant difference in cortisol increase after awakening among the three groups (ADHD+ODD, ADHD, and controls), and (ii) a significant interaction of group x time, reflecting that group differences in cortisol level depend on the time of day when samples were collected for these measurements. The influence of other factors that may modulate levels of arousal such as age, sex, pubertal stage, body mass index (BMI) (Adam, 2006; Oskis et al., 2009), and internalizing problems (such as depressive and anxiety symptoms) (Van den Bergh et al., 2008) was evaluated, also.

Methods

Subjects

Participants were 33 children (ages 6-12 years) diagnosed with ADHD-Combined Type and 33 sex- and age-matched normal developing control children selected within the same class as the child with ADHD. Control children had no formal psychiatric or medical diagnosis and were medication-free. Children with ADHD were recruited from a child psychiatric outpatient unit where they were diagnosed based on a child psychiatric evaluation (parents' history of the child's symptoms as well as information from teachers, and if necessary a school observation). Prior to participation, a structured interview for parents (Diagnostic Interview Schedule for Children, PDISC-IV) was used to confirm the clinical diagnosis of ADHD-Combined Type and to establish comorbid conditions (Shaffer et al., 2000). An ODD diagnosis was obtained in 22 children (of which two were also diagnosed with CD). This defined two ADHD subgroups (ADHD+ODD; n=22 and ADHD; n=11). Exclusion criteria were an IQ<80 (Wechsler Intelligence Scale for Children, WISC-III-R; Wechsler, 1991), autism spectrum disorder, chronic medical conditions, and any medication except for methylphenidate. Twenty-eight children with ADHD took methylphenidate, but all were medication-free at least 72 hours prior to participation to avoid confounding with an acute effect of methylphenidate that increases circulating cortisol (Volkow et al., 1995).

The Child Behaviour Checklist (CBCL; Achenbach, 2001) was used to screen for current behavioural and emotional problems; including internalizing problems that have been related to alterations in cortisol levels (Van den Bergh et al., 2008). This questionnaire, completed by parents, has good reliability and validity (Achenbach, 2001). It contains 112 items rated on a 3-point Likert scale (not at all to often) yielding broadband scales for internalizing (combines scales of withdrawn, somatic complaints and anxious/depressive behaviour) and externalizing (combines scales of delinquent and aggressive behaviour) problems. Pubertal stage and BMI were also assessed because of their impact on circadian expression of cortisol (Adam, 2006; Oskis et al., 2009).

Procedure

This study was approved by the Ethical Committee of the Ghent University Hospital, Belgium. After parents of children with ADHD provided written informed consent, the school and teacher were asked for their cooperation. Teachers selected three sex- and age-matched normally developing classmates without formal psychiatric of medical diagnosis, and if all parents provided written consent, one control was selected randomly to participate in the study.

We measured diurnal cortisol levels of the ADHD and control children in the naturalistic home and school environment during five consecutive days (three weekdays/two weekend days). The participants were randomly assigned to start with weekdays or weekend days, and this resulted in 18 children being evaluated from Tuesday evening to Sunday evening and 15 children from Friday evening until Wednesday evening. On the first data collection day, the cortisol sampling protocol was explained to parents and teacher, and children were trained in the saliva collection procedure. After five days, children received a reward (small toy selected by themselves plus an entrance ticket for a leisure park) for their participation.

Salivary Cortisol Sampling and Analysis

Saliva cortisol was collected using the "Salivette" device (Sarstedt®), which provides a non-invasive measure of the unbound -bioactive- cortisol fraction that is highly correlated with circulating plasma levels. Compared to venipuncture or saliva collection in a laboratory setting, saliva sampling in a naturalistic setting does not induce stress (Kirschbaum & Hellhammer, 1989).

Participants were instructed to collect five saliva samples at specific times across the day: directly after awakening (Cort1), 30 min post-wake time (Cort2), noon (Cort3), 4PM (Cort4), and 8PM (Cort5). Differences were expected in bed- and awakening times during weekdays and weekend days, so parents noted these times on each of the study days.

The "Salivette" consists of a cotton swab that participants chew gently for 1 min. To avoid known problems, participants were asked not to drink or eat sour products (low pH) or not to brush their teeth (blood contamination) 30 min before sampling. After saliva collection, the swab was transferred into a plastic tube and stored in the refrigerator at home until the end of the five days, when all tubes were collected. Parents or teachers wrote the sampling time on Cort1 and Cort2 tubes and, when deviating from the expected time, on Cort3, Cort4 and Cort5 tubes. Parents and teachers were asked to set an alarm to remind children of the cortisol collection during the day (Cort3/Cort4). To further enhance compliance and accurate reportage of sampling times, participants were told that accuracy of sampling times could be monitored from the samples in the lab. Samples were excluded when sampling time deviated >15 min from waking and expected hours. Of a total of 1650 cortisol samples, 90 samples (5%) were randomly missing due to forgetting, deviating sampling times or insufficient saliva collection.

Samples were centrifuged at 4°C (2000 g for 10 min) and stored at -26°C to maintain stability until assay. Samples were analyzed in two batches by the Brussels University Hospital, Department of Hormonology by radioimmuno assay (RIA, Diasorin, Italy), using a modification of an unextracted RIA method for serum cortisol. Briefly, 200 µL saliva was pipetted into the coat tube and incubated with ^{125}I cortisol for 45 min at 37°C. The modified cortisol assay had a range from 0.5-30 µg/L and within- and between-run coefficients of variation of <5% and <10%, respectively.

Statistical Analyses

Demographic variables (age, sex, BMI, pubertal stage), CBCL scores, and sleep-wake hours were compared between ADHD+ODD, ADHD, and control group using analysis of variance (ANOVA) or chi-square analysis as appropriate. Weekday and weekend sleep-wake hours were also compared using ANOVA.

To compare the awakening response between ADHD subgroups and control group, the area under curve (AUC=(Cort2–Cort1)x4) was calculated to estimate the average increase. To investigate the diurnal cortisol decline in ADHD+ODD, ADHD, and control groups, mixed model analysis was conducted with SAS PROC MIXED. Mixed models are

preferred over repeated measures ANOVA for the study of longitudinal data as they have greater flexibility to model time effects and correlation patterns between repeated measurements and handle missing data more appropriately (Gueorguieva & Krystal, 2004). The diurnal profile was based on four approximately equally spaced time points: awakening (Cort1), noon (Cort3), 4PM (Cort4), and 8PM (Cort5). For each of the four post-awakening time points, samples across days (up to 5 when there were no missing data) were averaged by the SAS program. Averaging data cancels out random day-to-day variation and increases precision. This can lead to an increase in effect size (ES), the standardized mean difference between groups (Cohen $d=(mean1–mean2)/SD_{pooled}$), which is independent of sample size but depends on precision of measurement (Swanson et al., 2001). ES values are defined as small (0.2), moderate (0.5), and large (0.8) to help interpret clinical relevance of statistically significant effects (Cohen, 1992). The distribution of cortisol concentrations showed positive kurtosis and skewness, so analyses were performed with the log-transformed values. The SAS Proc Mixed procedure requires the specification of models: Plausible covariance-pattern models (heterogeneous compound symmetry, heterogeneous autoregressive, and unstructured covariance patterns) were fitted, with or without inclusion of random intercept effects for subject and for day of evaluation (within subject). The best fitting mixed model was selected by likelihood ratio comparison tests. Analysis was performed with fixed effects of group (ADHD+ODD vs ADHD vs control), time (four time points per day), and group x time in a model controlling for day order (day1 to day5) and weekday vs weekend day. Possible confounders (age, sex, BMI, pubertal stage, and internalizing problems) were entered one by one, and those that did not significantly contribute to variations in cortisol levels were excluded from the model. To decompose the group x time interaction effect, two orthogonal contrasts were defined. The first was a contrast of the control group vs the overall ADHD group. The second was a contrast of the ADHD subgroups (ADHD+ODD vs ADHD). The mathematical relationship of time and cortisol level was additionally assessed by evaluating the linear, quadratic, and cubic effects for the main effect of time and for the group x time interaction.

Results

Descriptive Statistics

The ADHD+ODD, ADHD, and control group were not significantly different with respect to age, sex, pubertal stage, BMI, awakening and sleeping times. Weekday and weekend days were not significantly different for sleeping time (paired t(65)=-1.63; ns) but were for waking times (paired t(65)=-13.649; p<0.001). The average CBCL ratings for the ADHD subgroups were significantly higher than for the control group (see Table 1).

Table 1

Test Statistics of Demographic Variables, Awakening and Sleep Times, and CBCL Ratings

	Control	ADHD+ODD	ADHD	
	M(SD)/n(%)	M(SD)/n(%)	M(SD)/n(%)	$F(2,64)/\chi^2(2)$
Age	8.88(1.62)	9.09(1.54)	8.82(1.54)	<1
Sex (n)	26m (79), 7f (21)	17m (77), 5f (23)	9m (82), 2f (18)	<1
Pre-pubertal stage				
- Pubic hair stage (n)	26m (100),	14m (82),	9m (100),	4.55(m);
	6f (86)	5f (100)	2f (100)	1,08(f)
- Genital stage (n)	26m (100)	16m (94)	9m (100)	<1
- Breast stage (n)	6f (86)	4f(80)	2f (100)	<1
BMI	15.82(1.63)	17.12(2.13)	15.04(1.33)	3.06
Weekday sleep time	20:38(0:30)	20:16(1:10)	20:35(0:24)	1.48
Weekday awakening time	6:59(0:21)	6:52(0:24)	6:59(0:19)	<1
Weekend sleep time	21:04(2:43)	20:49(3:11)	21:37(0:36)	<1
Weekend awakening time	8:02(0:38)	8:05(0:43)	8:01(0:43)	<1
CBCL internalizing	46.33(9.28)	63.10(9.15)	62.09(7.74)	27.03***
CBCL externalizing	44.64(8.53)	86.95(7.70)	62.09(5.43)	66.51***

Note. ADHD+ODD=attention-deficit hyperactivity disorder with oppositional defiant disorder; ADHD=ADHD without ODD; M=mean; SD=standard deviation; n=number in sample; %=percentage of sample; m=males; f=females; CBCL=child behaviour checklist
***p<0.001

Cortisol Awakening Increase

The cortisol awakening response (increase from awakening to 30 min after awakening) was not significant between groups ($F_{(2,61)}=0.62$; $p=0.54$). Means, standard deviations, and effect sizes at Cort1/Cort2 time points are provided in Table 2. To evaluate whether the awakening response may be different for weekdays or weekend days, analyses were repeated for weekdays ($F_{(2,61)}=0.01$; $p=0.99$) and weekend days ($F_{(2,61)}=1.87$; $p=0.16$) separately, yielding similar results.

Table 2

Summary Statistics for Cortisol Concentrations (µg/L) on Five Time Points Across the Day, Averaged Across Five Days

| Time	Control M(SD)	ADHD+ODD M(SD)	ADHD M(SD)	Control vs ADHD ES	ADHD+ODD vs ADHD ES
Awakening	8.11(3.18)	8.53(5.10)	7.06(1.38)	0.02	0.39
30 min after awakening	9.01(2.34)	9.99(4.70)	8.61(1.88)	0.16	0.39
Noon	3.89(1.21)	3.32(0.73)	3.33(0.59)	0.83	0.02
4PM	2.97(1.01)	2.88(0.50)	3.04(0.77)	0.05	0.25
8PM	1.61(0.59)	1.29(0.50)	2.14(1.23)	0.04	0.91

Note. M=mean; SD=standard deviation; ES=effect size (Cohen *d*); ADHD+ODD=attention-deficit hyperactivity disorder with oppositional deviant disorder; ADHD=ADHD without ODD

Cortisol Daytime Decline

Variations in cortisol levels at the 4 post-awakening times across the day were best modeled using a heterogeneous first-order autoregressive covariance structure and a random intercept effect for subject. Age, sex, BMI, pubertal stage, and internalizing problems were excluded from the final model as these factors did not significantly contribute to variations in cortisol levels. For a model controlling for day of evaluation ($F_{(4,1166)}=0.74$; $p=0.57$) and weekday vs weekend day ($F_{(1,1166)}=3.87$; $p=0.05$), there was a significant effect of time ($F_{(3,1166)}=767.73$; $p<0.0001$) and group x time ($F_{(6,1166)}=4.05$; $p<0.001$), but no main effect of group ($F_{(2,1166)}=0.69$; $p=0.50$). Polynomial contrasts of the

time factor showed a significant linear effect (p<0.0001) reflecting a linear decline in cortisol levels from awakening to evening, a quadratic effect (p<0.001) reflecting a steeper decline in the morning than in the afternoon, and a cubic effect (p<0.0001). The orthogonal contrast of the overall ADHD group and the control group revealed that the linear (p=0.75), quadratic (p=0.26), or cubic (p=0.07) interaction components were not significantly different. The second orthogonal contrast -comparing the ADHD+ODD and ADHD subgroups- revealed a significant difference between groups in the linear component (p<0.001). The quadratic (p=0.20) or cubic (p=0.19) components of the interaction were not significant which may however be due to a lack of power to detect such differences. Despite the small number of participants in ADHD subgroups, the ADHD+ODD subgroup showed significantly higher morning and lower evening levels, resulting in a steeper linear decrease in cortisol levels throughout the day as compared to the ADHD subgroup. Comparable results were obtained in additional analyses where ODD symptoms were considered as a continuous dimension (published as online supplementary material). A visual representation of group differences in cortisol levels (μg/L), averaged across 5 days, is presented in Figure 1. Means, standard deviations, and effect sizes at each time point are provided in Table 2.

Figure 1. Group differences in cortisol concentrations across the day, averaged across five days.
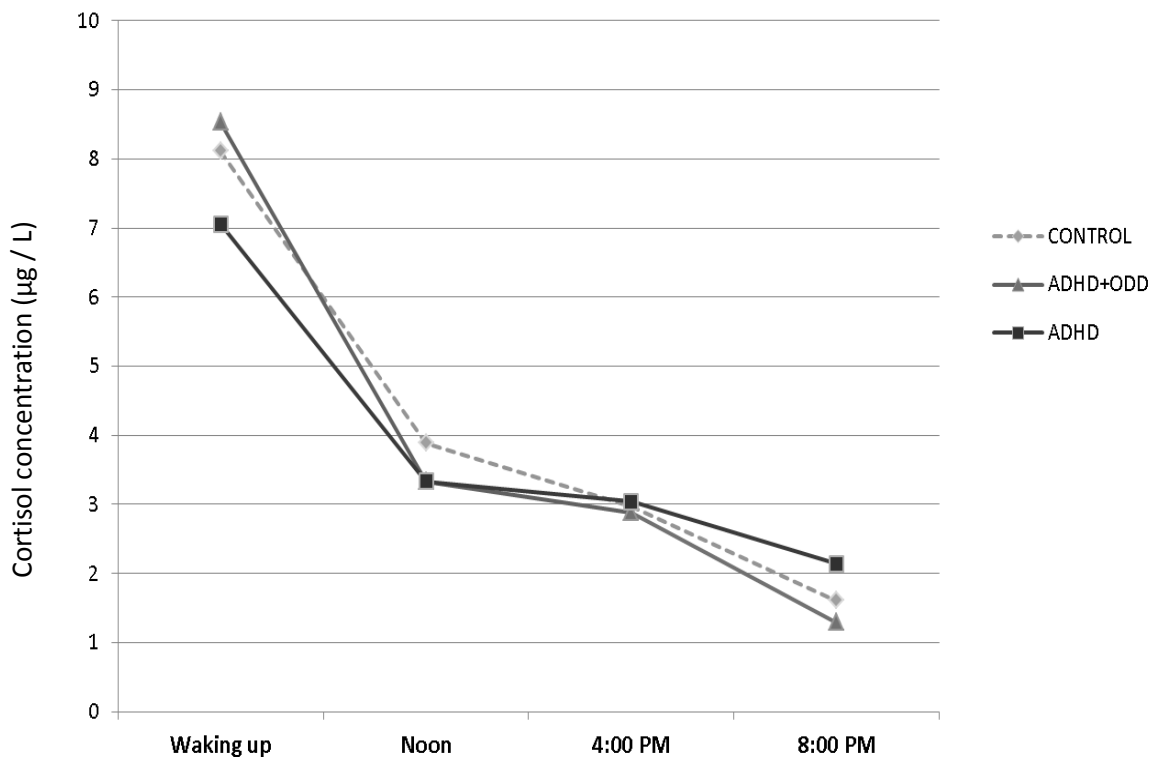
Confirmatory analyses of weekdays and weekend days separately were performed and revealed similar findings: the linear component of the group x time interaction for the ADHD+ODD and ADHD subgroups differed significantly during weekdays (p<0.01) and weekend days (p=0.01).

Discussion

To the best of our knowledge, this is the first study of cortisol and ADHD with such a large number (25) of observations for each individual, which were obtained over five days with five measurements across each day in ADHD children compared to age-matched controls. This study aimed to investigate whether variation in cortisol levels across the day would be consistent with the theory of an abnormal diurnal arousal pattern associated with ADHD (i.e., time-specific hypo- vs hyperarousal). We assessed (i) the cortisol awakening response (increase from awakening to 30 min after awakening), and (ii) the daytime decline (variations in intra-day cortisol levels based on four time points across the day: awakening, noon, 4PM, 8PM).

With respect to the awakening response, we found no evidence for group differences, which is partly in line with Freitag et al. (2009) who reported no different awakening response in children with ADHD but a significantly lower awakening response in children with ADHD+ODD. This discrepancy may be explained by methodological differences in timing of cortisol assessments; Freitag et al. (2009) assessed awakening response at four time points (0, 30, 45, and 60 min after awakening), while we had only two time points (0 and 30 min after awakening), and they did not assess the post-awakening pattern, while we assessed it across the entire day.

With respect to the daytime decline, we found a significant interaction of time and group; orthogonal contrasts showed this effect was related to across-the-day differences between the ADHD subgroups and not to an overall difference between the ADHD group (average of the two subgroups) and the control group. Most studies in children with ADHD reported time-specific differences in cortisol levels (Blomqvist et al., 2007; Kaneko et al., 1993). This discrepancy may be explained by methodological differences in diagnosis: these

studies did not subgroup ADHD cases based on the presence or absence of ODD, which is very common on most clinical samples. Since the two subgroups (ADHD+ODD and ADHD) showed differential patterns, subgroup differences may have existed but cancelled each other. Studies in general population samples have shown a lower morning-to-afternoon ratio associated with the presence of attention problems (Susman et al., 2007), which partly support our findings of a flattened decline in the ADHD subgroup.

Our results support the hypothesis that arousal-related circadian rhythms may be altered in children with ADHD. Since we found that alterations in the diurnal cortisol pattern in our ADHD sample are based on the presence or absence of comorbid ODD, we can extend the hypothesis by suggesting differences in the pathophysiology of ADHD+ODD and ADHD. In the regulation of attention, behaviour, and emotion, differential neurophysiologic effects of cortisol have been described in the HC, amygdala, and PFC as these brain regions contain different cortisol receptors (Hastings et al., 2009). Whereas the HC and amygdala contain both mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), the PFC only contains GR (Sanchez et al., 2000). Binding on MR occurs for most of the circadian cycle as these receptors have a high affinity for cortisol. GR on the contrary have a lower affinity for cortisol resulting in increased cortisol binding only when circulating cortisol rises: for example, during peak moments of circadian activity, i.e. the 'wake-up' period (Reul & Kloet, 1985). Therefore, we propose that the action of cortisol in these brain regions is highly time-dependent and differentially altered in children with ADHD+ODD and ADHD.

This contrasts with theoretical frameworks that have defined ADHD and ODD in terms of hypo-arousal deficits (Raine, 1996; Sonuga-Barke et al., 2010), largely ignoring circadian effects on arousal. Rather than being chronically hypo-aroused, our findings suggest the subgroups of children with ADHD+ODD and ADHD may be hypo- or hyperaroused at different times of day. If these findings could be replicated in larger samples, this knowledge on time-of-day effects in cortisol level may guide timing of interventions with arousal level as a presumed target. Though time-of-day effects on different modalities of interventions for ADHD have not been assessed systematically (Swanson et al., 2004), we hypothesize that the ADHD+ODD and ADHD subgroups may benefit most from different treatment modalities at different times of day. For example, the mechanism of action of stimulant medication has predominantly been associated with an

increase in arousal, and some speculate that its therapeutic effects are due to the correction of a state of underarousal. This leads to the hypothesis that morning treatment with medication may be more beneficial for children with ADHD than with ADHD+ODD. In contrast, the mechanism of action of non-pharmaceutical treatments such as relaxation or mindfulness have predominately been associated with a decrease in arousal, suggesting that children with ADHD+ODD may benefit most from this intervention in the morning rather than in the afternoon/evening.

Although this study has some clear strengths associated with the evaluation of intra- and interday cortisol variability, some limitations must be taken into account. First, salivary cortisol samples were collected in the naturalistic environment of children, which resulted in some non-compliance. Due to financial constraints, it was not possible to use electronic monitoring devices to assess time of saliva collection, which would be a good addition to future studies. Second, the overall sample size in this study was limited leading to small sample sizes for the evaluation of the clinical subgroups (ADHD+ODD and ADHD). Third, this study did not include subjects with ODD without ADHD. It is not clear whether differences found in ADHD+ODD and ADHD subgroups are specific for ADHD, ODD, or the comorbid condition. Fourth, we did not control for activity levels which may have influenced cortisol concentrations and which may have differed for the ADHD and control groups in similar school settings (same classrooms) during the weekdays or in different home settings during the weekend days. Fifth, the study lacked of an objective test of arousal (i.e., multiple sleep latency test) that could have been coupled to measure of cortisol. Sixth, we did not assess current nor previously experiences of stress, which have been related to higher cortisol levels. In future studies, it may be valuable to document stressful experiences (e.g., prenatal exposure to teratogens and stress, separation, and abuse) that may cause long-lasting or even permanent alterations of the HPA axis function by affecting steroid receptors in the PFC and HC (McBurnett et al., 2000; Meaney et al., 1985). Finally, we did not adjust for effects of age, sex, BMI, and pubertal stage, which were not significantly related to cortisol levels in our study but may be present and operate to confound our results.

Conclusion

In summary, in our analyses of cortisol levels within- and across-days, we observed a significant ADHD subgroup x time interaction reflecting a reversal of a group difference in cortisol levels from the morning to evening. This suggests that the ADHD subgroup may be relatively hypo-aroused in the morning but hyperaroused in the evening, while the ADHD+ODD subgroup may be relatively hyperaroused in the morning and hypo-aroused in the evening. Though further research is recommended to validate our findings in larger samples and to explore the association of ADHD with other comorbidities, knowledge on time-specific arousal deviations in ADHD subgroups may guide the timing of arousal-based treatments.

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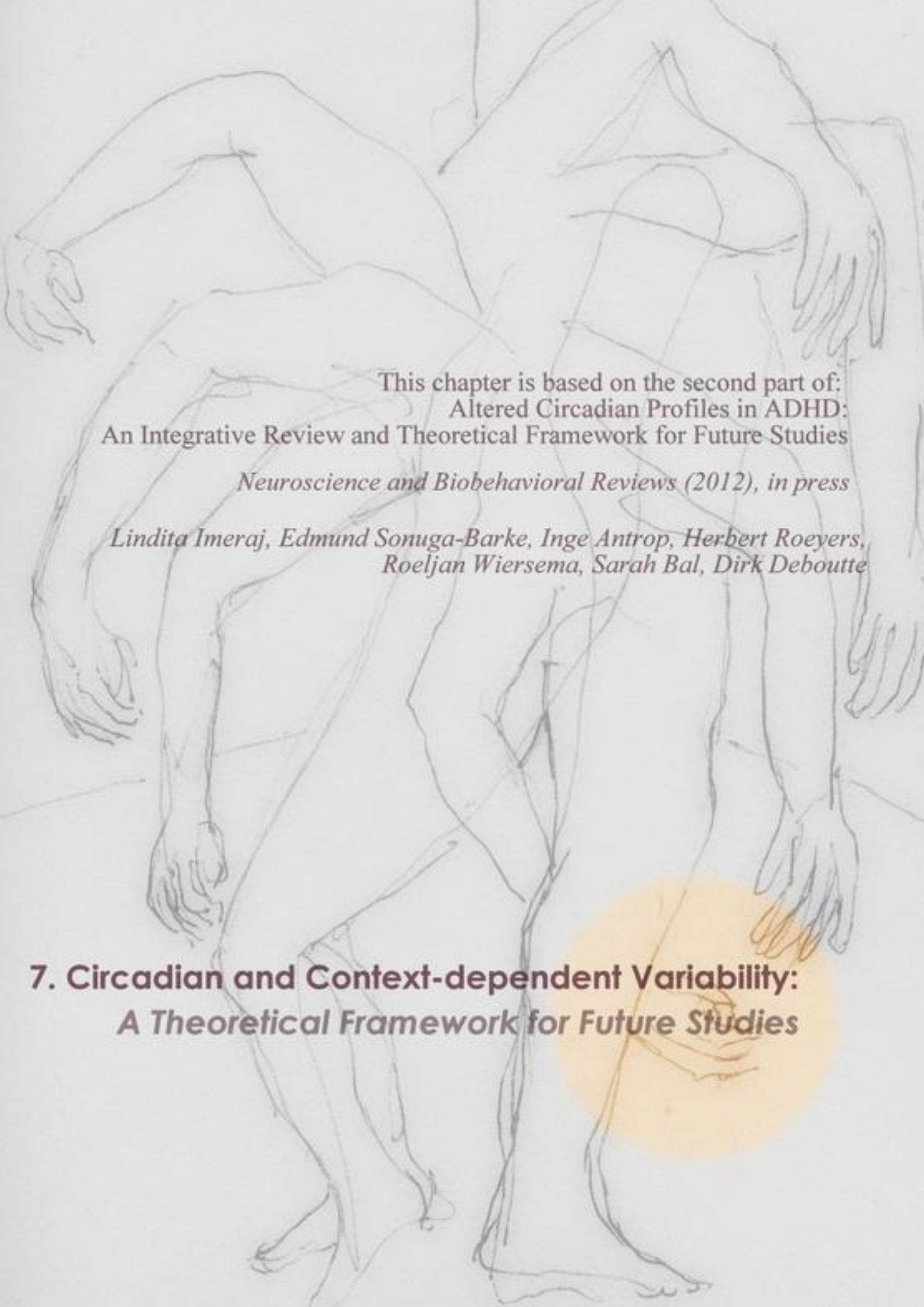
PART B: Disrupted Circadian Cortisol Profiles in ADHD

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Part C

ADHD as a function of Context x Time of day

In this part, we provide a neurobiological working hypothesis that considers both contextual (part A) and circadian (part B) effects on arousal in ADHD. This interactive model suggests a central role for the locus coeruleus in linking ADHD to circadian and other arousal-mediated effects. Such theoretical developments could serve as a framework for future research.

7. Circadian and Context-dependent Variability:
A Theoretical Framework for Future Studies

Abstract

In ADHD the best evidence of arousal-related dysregulation comes from studies of the impact of changing environmental context on behavior and information processes (see *part A* of this dissertation). These have usually been interpreted in the light of state regulation deficits using cognitive energetic models. These models did not consider time of day effects in arousal so far despite the fact that circadian disruptions are reported in several studies (see *part B* of this dissertation).

In the current chapter, we suggest an extension of models of altered arousal mechanisms in ADHD encompassing both cognitive energetic effects due to altered responses to changes in environmental context and disrupted patterns of spontaneous circadian activity across the day. In this neurobiological model, we highlight the potential role of the locus coeruleus (LC) disruption in ADHD as a biological mediator of both context specific cognitive energetic effects and context independent circadian effects. Based on this perspective specific recommendations for future research are presented.

Keywords: ADHD, arousal, context, circadian, suprachiasmatic nucleus, locus coeruleus

1. 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 attention-deficit/ hyperactivity disorder (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 locus coeruleus (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 2).

1.1. 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 (suprachiasmatic nucleus; 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). An illustration of the SCN-DMH-LC circuit is provided as supplementary material (p. 230).

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 (See illustration 2 provided as supplementary material; p. 231). 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.

1.2. 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.

1.3 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).

1.4. 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 2.1.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.
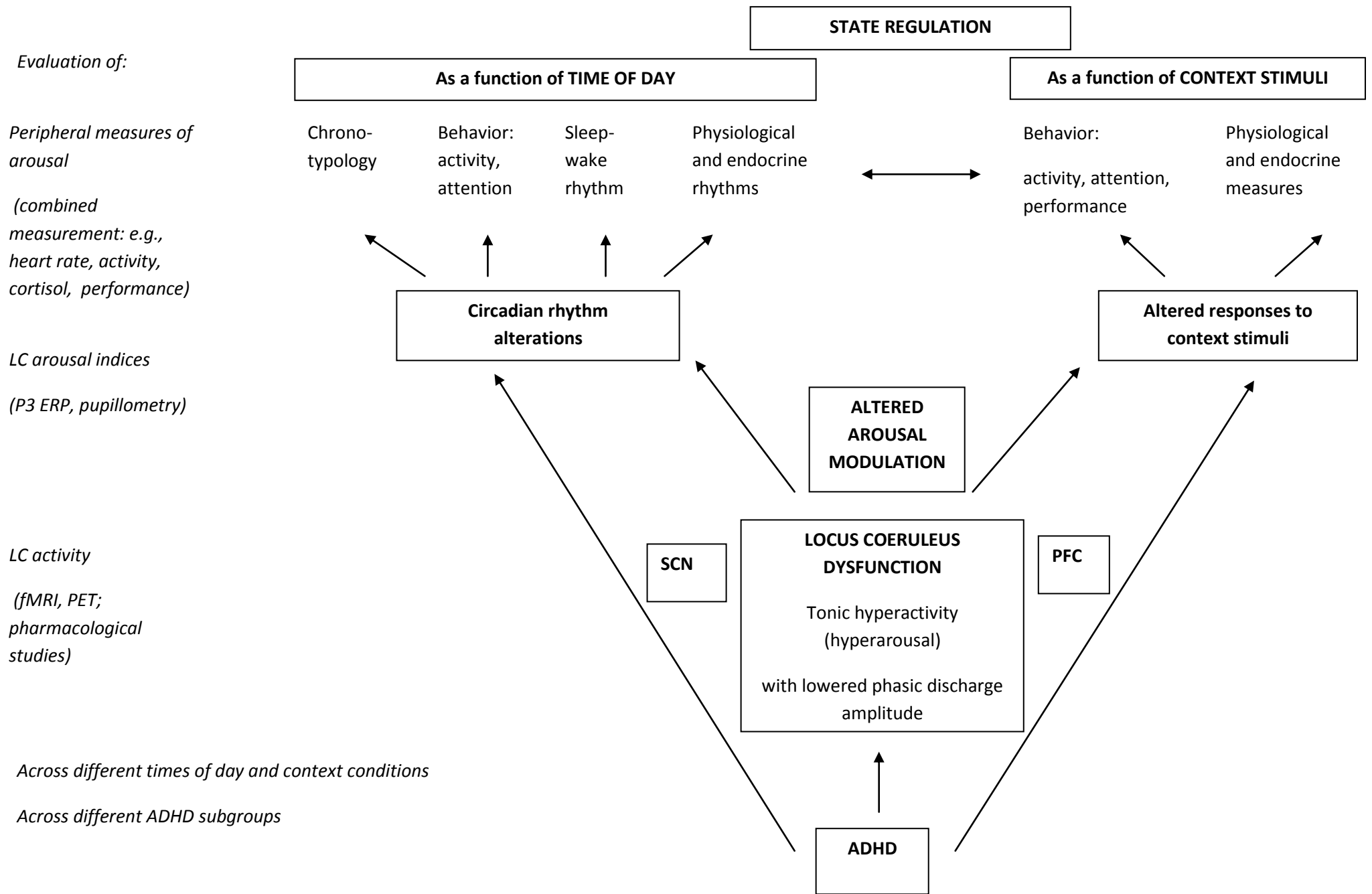
STATE REGULATION

Evaluation of:

As a function of TIME OF DAY

As a function of CONTEXT STIMULI

Peripheral measures of arousal

(combined measurement: e.g., heart rate, activity, cortisol, performance)

Chrono-typology

Behavior: activity, attention

Sleep-wake rhythm

Physiological and endocrine rhythms

Behavior: activity, attention, performance

Physiological and endocrine measures

Circadian rhythm alterations

Altered responses to context stimuli

LC arousal indices

(P3 ERP, pupillometry)

ALTERED AROUSAL MODULATION

LC activity

(fMRI, PET; pharmacological studies)

SCN

LOCUS COERULEUS DYSFUNCTION

Tonic hyperactivity (hyperarousal)

with lowered phasic discharge amplitude

PFC

Across different times of day and context conditions

Across different ADHD subgroups

ADHD

Figure 1. Working hypothesis on LC-mediated arousal dysfunction in ADHD linking context driven cognitive-energetic and context-independent circadian-based alterations

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).

2. Proposals for Future Study of Circadian (and Contextual) 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.

2.1. 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. Multiple sleep latency test (MSLT) represents another option for the evaluation of daytime sleepiness and polysmonography (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, dim light melatonin onset (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.

2.2. 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 hypothalamic-pituitary-adrenal (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.

2.3. 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 (oppositional defiant disorders (ODD), conduct disorders (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).

3. Conclusion

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.

Supplementary material

Illustration 1.1. The SCN-DMH-LC circuit as provided by Aston-Jones (2005). Circuit for circadian regulation of locus coeruleus (LC) and arousal.
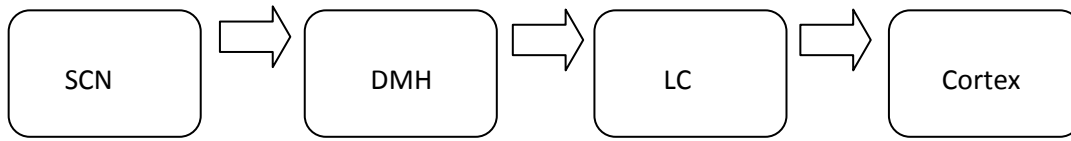
*Note.* DMH = dorsomedial hypothalamic nucleus; SCN = suprachiasmatic nucleus. Aston-Jones G, personal data.

Illustration 1.2. The link between the SCN and DMH to promote wakefulness is illustrated by the figure below.

Adapted from Saper, Scammell and Lu (2005). Hypothalamic regulation of sleep and circadian rhythms. Nature 437, 1257-1263.
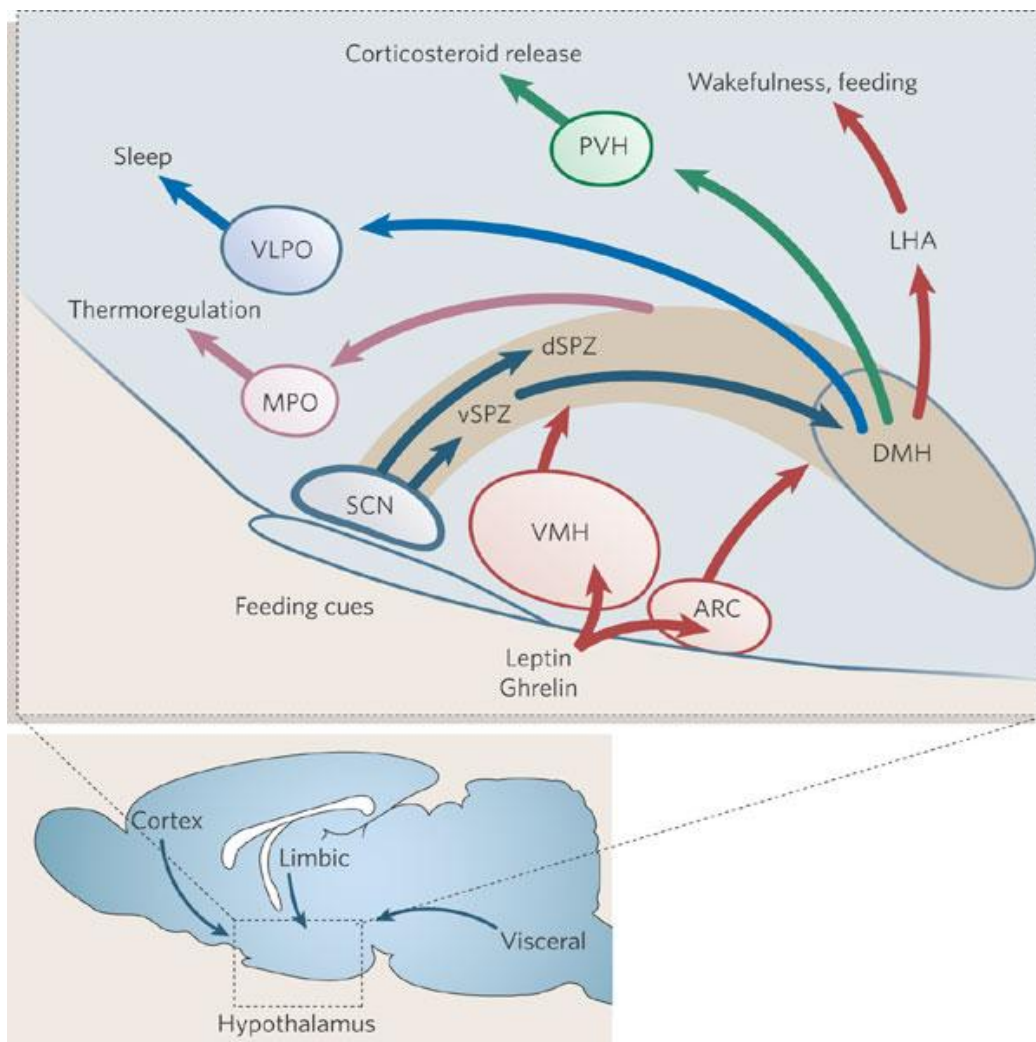
Note. The **suprachiasmatic nucleus (SCN)** serves as a biological clock, but has few outputs to sleep-regulatory systems. Most of its output goes into the region in light brown, which includes the ventral (vSPZ) and dorsal (dSPZ) subparaventricular zone, and the **dorsomedial nucleus of the hypothalamus (DMH)**. Neurons in the vSPZ relay information necessary for organizing daily cycles of wake-sleep, whereas dSPZ neurons are crucial for rhythms of body temperature. Outputs from the SPZ are integrated in the DMH with other inputs, and DMH neurons drive circadian cycles of sleep, activity, feeding and corticosteroid secretion. Cycles of body temperature are maintained by dSPZ projections back to the medial preoptic area (MPO), whereas the DMH is the origin of projections to the VLPO for sleep cycles, to the corticotropin-releasing hormone (CRH) neurons of the paraventricular nucleus (PVH) for corticosteroid cycles, and to the **lateral hypothalamic (LHA)** orexin and melanin-concentrating hormone neurons for wakefulness (LHA has 'excitatory' projections to the **locus coeruleus (LC)** in the brain stem) and feeding cycles. The integrative steps in the SPZ and DMH allow circadian rhythms to adapt to environmental stimuli, such as food availability (for example, leptin and ghrelin action via the ventromedial (VMH) and arcuate (ARC) nuclei), as well as visceral sensory inputs, cognitive influences from the prefrontal cortex and emotional inputs from the limbic system (inset).

Illustration 1.3. Orexin pathways from the hypothalamus to the LC and from the LC to the cortex promoting wakefulness are illustrated by the figure below.
Adapted from Scammell and Saper (2007). Orexins: looking forward to sleep, back at addiction. Nature Medicine 13, 126 – 128.
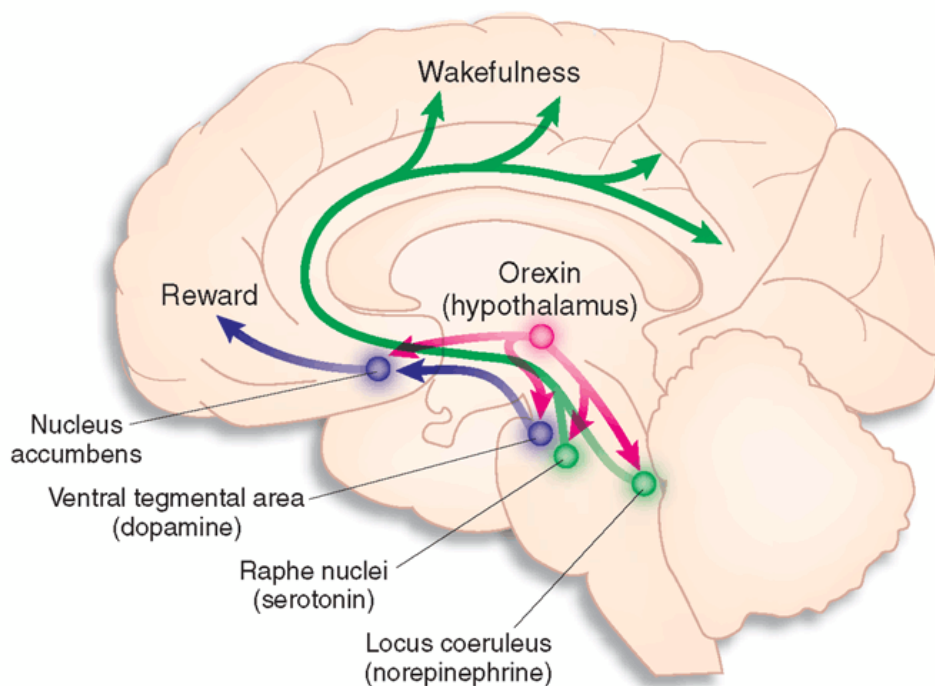
Note. The orexin neurons innervate and excite many brain regions that drive arousal and attention, including the locus coeruleus and the dorsal raphe.

Illustration 2. The Yerkes-Dodson relationship as published by Aston-Jones and Cohen (2005).
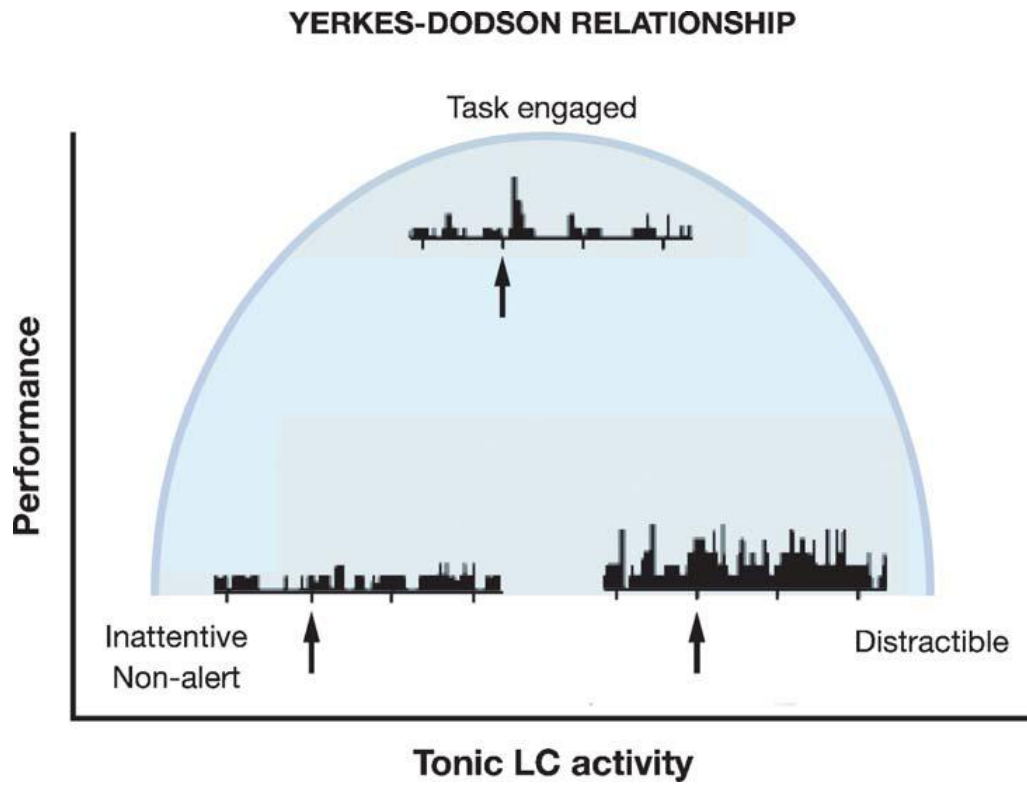
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8. General Discussion

In general, this dissertation aimed at investigating the impact of *situational conditions (Part A)* and *circadian characteristics (Part B)* on the expression of behavioural symptoms and arousal modulation problems in children with attention-deficit hyperactivity disorder (ADHD). To pursue ecological validity and generalisability of findings, we observed elementary school children with ADHD and typically developing peers (age-, sex-, and class-matched pairs) in their naturalistic school and home environment. We expect that the identification of problem behaviour as a function of environmental triggers and difficult times of day will lead to context- and time- specific interventions that may improve everyday functioning and outcome in this population. *In part C,* we additionally provided a neurobiological working hypothesis that considers both context- and circadian- dependent influences. This model is an extension of current state-regulation deficit theories that could serve as a framework for future research on behavioural variability in ADHD. In Chapter 1, the concept of ADHD variability (as a function of context and time of day) was introduced and the design and research goals of this dissertation were addressed.

ADHD Behaviour as a Function of Context (Part A)

Laboratory studies have shown that ADHD children's disruptive behaviour and performance deteriorates in certain contexts as predicted by a number of theories of ADHD – especially those that emphasize the role of context-dependent dynamic processes in ADHD pathophysiology (Sonuga-Barke et al., 2010), such as delay aversion (Sonuga-Barke et al., 2008); state regulation deficits (Sergeant & Van der Meere, 1988, 1990); and the drive for optimal simulation (Zentall, 1975). However, little is understood about the practical implications of these sorts of context effects on everyday behaviour and functioning in naturalistic environments (Lauth, Heubeck, & Mackowiak, 2006; Barkley & Fischer, 2011).

Despite the fact that observational research is time-consuming and labour-intensive, and therefore has a high financial cost, direct observation of children with ADHD in their ecological setting is recommended (Antrop et al., 2005a): (1) laboratory findings are seldom representative for the home and school situation (Antrop et al., 2000; Danforth, Barkley, & Stokes, 1991; Tryon, 1993; Zentall & Zentall, 1976), (2) behaviour is more variable when observed within this context (Tryon, Pinto, & Morrison, 1991), and (3) ADHD behaviour is

particularly expressed within a familiar environment rather than in situations that provoke novelty or fear (Teicher et al., 1996; Zentall, 1975). Measuring and quantifying behaviour can allow us to reliably estimate and compare across children and settings, and to determine the extent to which other factors influence it.

Since ADHD behaviour at school represents one of the most potent factors predicting school-related and broader patterns of achievement and functioning (Barkley et al., 2006; Fergusson & Horwood, 1995), the classroom represents an environment of choice to observe behavioural symptoms in children with ADHD. In the current dissertation, we tested the prediction that certain classroom conditions would have a greater impact on the behaviour of children with ADHD as compared to non-ADHD classmates. Therefore, we observed 31 children with ADHD and 31 age- and sex-matched typically developing classmates in their naturalistic class environment during 2 consecutive days.

Several standardized observation coding schemes are currently available (for a review, see Volpe et al., 2005); however, none of them contains information regarding the various factors that potentially influence classroom observations. Our coding scheme was developed specifically for this study, i.e., the Ghent University Classroom Coding Inventory (GUCCI). This inventory is partly adapted from previously published coding schemes (Abikoff, Gittelman, & Klein, 1980; Blatchford, Bassett, & Brown, 2005; Lauth et al., 2006; Milich & Landau, 1988; Porrino et al., 1983; Tsujii et al., 2007). It includes several situational condition codes and different classroom behaviours which were continuously coded in Observer (Noldus, version 9). Video material was imported in this professional software, which has the advantage that it can select each specific contextual condition to analyze the duration of a child's behaviour (% of time) during that period. Eleven undergraduate psychology and medical students were intensively trained to work with Observer and were supervised by the main researcher to code idle time condition (one student), hyperactivity/ noisiness (two students), social behaviour (two students), or transition periods (one student), class group structure/academic content type (one student), on-task behaviour (two students), teacher's supervision (two students). Observers were blind to the diagnostic status of the children. Inter-observer variability between the students and the main researcher was calculated using Cohens' kappa for categorical variables. Based on Watkins and Pacceco (2000), agreement was excellent for idle time ratings (k = .99), transitions (k = .98), hyperactivity (k = .91 to.97),

noisiness (k = .96 to.99), class group structures (k = 0.99), academic content types (k = .95), teacher's supervision (k = .99 to 1.00); and very good for social behaviour (k =.74 to .79) and child's task-related attention (k = .77 to .84).

Summary of Findings

Chapter 2 investigated whether the impact of classroom "idle time" – periods of low stimulation, low structure, and delay – on disruptive classroom behaviour (hyperactivity, noisiness, and disruptive social behaviour) was higher in children with ADHD as compared to their typically developing peers. Children with ADHD showed more disruptive behaviour in general, which validated the coding system developed for the study. Irrespective of instructional condition, the classroom is an environment requiring high levels of self-regulation (Barkley, 1997), motivation (Sonuga-Barke, 2005), and cognitive and information processing skills (Sergeant, 2000). This setting is therefore likely to be especially demanding for ADHD children who often have deficits in these domains (Abikoff et al., 2002; Junod et al., 2006). However, consistent with different theoretical models, problematic levels of hyperactivity and noisiness (i.e., core symptoms of ADHD), but not social behaviour, were more exacerbated in children with ADHD than in their typically developing classmates during classroom idle time. As idle time is common during an average school day (12% of the time), it is a primary focus of concern. The failure to engage effectively in, and operate efficiently in, a delay-rich and low stimulation environment may reduce the development of organizational skills and strategies (Sonuga-Barke, 2005), which over time contributes to academic failure in children with ADHD (Fergusson & Horwood, 1995).

In chapter 3, we investigated whether different measures of task-related attention (i.e., time on-task, attention span) in children with and without ADHD differed across specific instructional contexts within a whole school day. We expected not only a significant interaction effect of class group structures and academic content types (inclusive instructional transition periods) by diagnostic group, but also different levels of individual teacher supervision in children with ADHD, as teachers are supposed to adapt the classroom environment to the child's needs. Though children with ADHD generally displayed lower on-task levels, specific conditions such as whole group teaching, individual work, instructional

transitions, and highly academic tasks exacerbated attention problems in children with ADHD as compared to their typically developing peers. These conditions may interact with specific deficits in self-regulation (Barkley, 1997), information-processing (Sergeant, 2000), and motivation (Sonuga-Barke, 2005) associated with the condition. These deficits may be difficult to compensate for in the normal classroom as attention problems seen persisted despite overall more teacher support of children with ADHD.

Current Limitations

This study had many strengths especially relating to its naturalistic (ecologically valid) observational design, the sampling over large periods of the day so that different instructional conditions (inclusive idle time, transition periods, and individualized teacher supervision) could be assessed using a reliable coding scheme, and a relatively large sample size. However, there were some limitations. *First,* the naturalistic class environment represents a less-standardized, less-controlled setting as compared to the laboratory context. It was not possible to control for every aspect of stimulation or structure within the environment. The camera, the presence of the examiner, additional noise, and unexpected interference may have influenced the results. However, as children with and without ADHD were observed simultaneously in the same classroom, it is reasonable to assume that these effects were similar for both groups of children. *Second*, despite their ecological nature, observations cannot be generalized to all settings. Current findings relate to Flemish regular elementary classrooms and may therefore not be representative for other world parts, special education settings, or home environments. *Third,* the operationalization of several concepts in the current studies may differ from this applied in controlled laboratory tasks. For example, we considered idle time as a proxy measure for the 'delay aversion' construct (chapter 2) and mean on-task interval duration for attention span (and relatedly attention shifts) (chapter 3). *Fourth,* despite observations during a longer time period, the occurrence of some conditions was relatively small in the naturalistic setting. For example, the use of specific instructional strategies such as small interactive group work (chapter 3) and supplementary tasks (as an alternative for idle time; chapter 2) was too limited to allow more detailed analyses. Also baseline rates of teacher supervision in the normal class

environment were low overall limiting further analyses of teacher quality in relation to contextual demands (chapter 3). *Finally*, the finding of overall higher levels of supervision in the ADHD group restricted generalization of our findings. We propose that a semi-experimental study, in which not only class context conditions but also levels of teacher supervision are similar for both groups and sufficiently taking place, would be helpful to fully explore the effect of specific (combinations of) instructional conditions and teachers' practices on classroom attention and disruptive behaviour in children with and without ADHD.

Clinical Implications

Despite some methodological limitations related to the observation in naturalistic settings, the current findings may contribute to a better understanding of the dynamics of 'real world' class environments that may guide further development of teacher strategies and academic interventions (Barkley, 2007; DuPaul, 2007; Greene, 1995). Though environmental conditions are not assumed to be causal by themselves, they may interact with specific (causal) deficits in ADHD (Barkley, 2007). Tackling these triggers may decrease classroom disruptive behaviour and increase attention levels in ADHD and therefore improve academic outcome and socio-emotional well-being in this vulnerable population (Hoff & DuPaul, 1998). Given that children with ADHD suffer when confronted with waiting situations, one way to reduce disruptive behaviour could relate to the anticipation of the challenges of idle time situation by for example proposing short alternative activities. Also the special structuring of classroom transition periods has been proven to be an effective way of reducing disruption (Lee, 2006). Though only limitedly used in daily teaching practice, it seems that working in small cooperative learning groups may increase task-related attention in children with ADHD –irrespective of extra individualized teacher supervision. It is not clear to what extent peer interactions in small groups have influenced behaviour in our sample of children with ADHD, but favorable effects of peer tutoring interventions have been described (DuPaul et al., 1998).

Some high-risk conditions such as highly academic tasks are mandatory in the regular curriculum and, during these situations, tempering problematic behaviour in children with

ADHD remains an enormous challenge. Next to structural adaptations such as suggested above, supportive teacher behaviour represents a prime target for intervention as increased supervision was related to better attention processing in both children with and without ADHD. However, our results indicated that children with ADHD were less attentive despite 'overall' higher supervision. The currently observed amount of teacher supervision in children with ADHD may thus still not be sufficient to increase on-task levels during high demanding tasks: this group of children was previously reported to be less able to benefit from a close teacher relationship (Baker, 2006). Yet, teachers did not further increase their individual support during high-demanding academic assignments as compared to other settings to –at least partly- approach the specific child's needs. As observed individual supervision levels are relatively low during an average school day, an additional increase in supervision in children with ADHD in these specific contexts as compared to less demanding ones (not 'overall') may still have a positive effect. These observations suggest that ways to improve the impact of teacher supervision need to be considered (Baker, 2006). Despite their high needs for encouragement and reward (Luman, Tripp, & Scheres, 2010; Sonuga-Barke, 2003), preliminary analyses of our observation data suggested that children with ADHD receive three times more negative remarks than positive feedback, whereas this "balance" is the opposite in their typically developing peers. Even more alarming was our finding that this balance remained negative when children with ADHD were on-task as expected by the teacher (Moreaux et al., 2011).

Our request to realize such adaptations in an instructional context and teacher behaviour may run into practical problems in today's regular classrooms. A conflict may arise between, on the hand, the child with ADHD and his/her specific needs (asking for extra support to organize behaviour) and, on the other hand, the regular educational system (imposing learning goals for children within a typically developing range). Struggling with this controversy, teachers may experience frustration and a lack of time and training to implement structural modifications. The increasing number of pupils in today's regular classrooms may impede further augmentation of individualized teacher supervision. Therefore, it might be possible that the normal classroom is not the ideal setting for ADHD and that different teaching approaches within a special setting might be needed. It would however be of large interest to explore the impact of different 'qualitative' teacher

strategies such as proactive teacher practices (Ervin et al., 1998) and the use of explicit rules with clear consequences for non-compliance (Emmer & Stough, 2001) to more effectively increase attention levels and decrease disruptive behaviour in children with ADHD within the regular classroom in order to improve long-term outcome. For example, in Flanders, the implementation of an ADHD tool kit for use in elementary schools has currently been tested to evaluate the feasibility of this "child-teacher game" and its impact on class functioning in children with ADHD (Danckaerts & Dewitte, 2009).

Arousal Dysregulation in ADHD as a Function of Time (Part B)

Several theoretical models have explained hyperactive, impulsive, and inattentive symptoms in ADHD in terms of arousal modulation deficits (hypo- and hyperarousal) (Sergeant & Van der Meere, 1990; Sonuga-Barke et al., 2010; Zentall & Zentall, 1983). Despite cumulating evidence on the role of circadian rhythms in the regulation of arousal (Silver & LeSauter, 2008), such time-of-day effects are not considered in current ADHD models. However, in clinical practice, spontaneous fluctuations in ADHD behaviour over time and sleep-wake problems are frequently reported by individuals with ADHD or their parents, even though such 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 & 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 similar to previous reports in other psychiatric disorders. 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.

To investigate whether a relation between behaviour/ arousal problems and time could be supported in ADHD, we first reviewed published studies on time-of-day effects in ADHD considering different research domains; i.e., (i) time-of-day effects on behaviour and activity; (ii) *morningness-eveningness* chronotypology; (iii) sleep/wake rhythms; and (iv) rhythmicity in neuroendocrine and neurophysiological responsiveness (chapter 4). We then

designed a study to investigate whether heart rate (chapter 5) and cortisol (chapter 6) profiles under natural environmental conditions differed in unmedicated children with ADHD as compared to normal control children. Despite high inter- and intra-day variability in these arousal-related circadian measures, to the best of our knowledge, longer-term evaluations (5 days) were not available in children with ADHD up till now, though recommended by several authors (Bartels et al., 2003; Edwards et al., 2001; Houtveen & de Geus, 2009; Schulz et al., 1997).

Summary of Findings

Chapter 4 included a literature review, which provided initial support for disrupted circadian rhythms in ADHD with respect to different research areas. 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 between ADHD and 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 notion 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 dim light melatonin onset (DLMO) in a subgroup of subjects with ADHD and chronic sleep onset insomnia, which improved after melatonin treatment. Second, on the behavioural 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 behaviour 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 be established. 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.

In chapter 5, we presented the only study available in children with ADHD considering a longer-term evaluation of heart rate with simultaneous activity registration. During a 5-day measurement, we expected that heart rate levels in the ADHD group would differ from the non-ADHD group as a function of time. Though heart rate levels were overall higher in children with ADHD as compared to controls, these effects were particularly expressed during the night and the afternoon. Therefore, circadian (dys)regulation may be important in clarifying this autonomic imbalance in ADHD. Nighttime tachycardia in this group could not be explained by nighttime activity levels or comorbid externalizing/ internalizing problems.

Chapter 6 investigated whether diurnal cortisol profiles in children with ADHD were different from their typically developing peers using a 'full circadian' longer-term evaluation. We found a time-specific disruption of diurnal cortisol activity in children with ADHD associated with the presence or absence of ODD comorbidity: the ADHD with comorbid ODD subgroup showed relative hyperarousal in the morning and hypo-arousal in the evening, whereas the ADHD without ODD subgroup showed an opposite pattern with relative hypo-arousal in the morning and hyperarousal in the evening. If findings are replicated in larger samples, this may lead to a better understanding of arousal mechanisms involved in ADHD not only with and without ODD but also with other comorbidities.

The somewhat divergent findings for heart rate and cortisol in ADHD may relate to the asymmetric relation between stress and arousal mechanisms as described by Pfaff et al. (2007): stimuli causing stress are theorized to cause arousal, but inversely, 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 hypothalamic-pituitary-adrenal (HPA) axis (e.g., cortisol) is only activated in stressful (chronic) conditions.

Current Limitations

Most currently available studies on time-of-day effects in ADHD were not designed for this purpose, using only a limited number of arousal-related circadian measures during relatively short observation periods. To the best of our knowledge, the heart rate and cortisol studies included in this thesis were the first longer-term evaluations designed to assess diurnal arousal profiles in children with ADHD in their naturalistic home and school environment. Despite some clear strengths associated with the investigation of intra- and interday variability in these measures and the ecological validity of the findings, some limitations must be taken into account. *First,* as studies took place in the naturalistic environment of children, missing data were inevitable. With respect to cortisol sampling, this was due to some non-compliance with sampling (chapter 6). With respect to heart rate, devices were not waterproof so that no data were available during bathing and swimming (chapter 5). *Second,* activity levels may have influenced our data. In our cortisol study (chapter 6), we did not control for activity levels. As activity may have differed for the ADHD and control groups, this may have affected our results. In our heart rate study (chapter 5), we simultaneously registered 24-hour activity patterns, but we did not systematically assess the amount of (regular) physical training, which is known to lower resting heart rate levels. Therefore, we cannot exclude the possibility that such activities have affected heart rate in our control more than in our ADHD group. *Third,* age, sex, body mass index (BMI), and pubertal stage have been reported to influence heart rate and cortisol levels. We did not systematically adjust for such effects as most of these factors were not significantly related to heart rate and cortisol levels in our study (except for age in heart rate analyses) but may be present and operate to confound our results. Then again, ADHD and control group were age- and sex-matched and most children in our sample were pre-pubertal without evidence for differences in pubertal stage and BMI between the ADHD and control group. *Fourth,* the confounding effect of stimulant medication must be considered as significant increases in heart rate, especially during the first 6 months of treatment, have been reported (Daniels, 2009). Although all participants were free from medication at least 72 hours prior to participation, to date, it is not sure whether fast-release preparations of methylphenidate could still have influenced cardiovascular functioning. In this study (chapter 5), day-to-day variability in heart rate levels however showed no decrease in the effect pattern from day

one to day five. Additional analyses showed that midnight heart rate levels were significantly higher on day 5 than on day one (p < 0.01), reducing the possibility that our findings can be explained by longer-term effects of stimulant medication. *Fifth,* we did not assess current and prior experiences of stress, which have been related to higher heart rate and cortisol levels. Accumulated stress is suggested to cause anomalies in heart rate, which could be an early peripheral marker of latent asymptomatic and undiagnosed comorbid emotional disorders (Tonhajzerova et al., 2009). In future studies, it may be valuable to document stressful experiences (e.g., prenatal exposure to teratogens and stress, separation, and abuse) that may cause long-lasting or even permanent alterations of the HPA axis function by affecting steroid receptors in the prefrontal cortex (PFC) and hippocampus (HC) (McBurnett et al., 2000; Meaney et al., 1985). *Finally,* dysregulation of the autonomic nervous system and the HPA-axis has been related to psychiatric disorders other than ADHD (Dietrich et al., 2007; Lorber, 2004; Ortiz & Raine, 2004). In our study, we looked at confounding effects of psychiatric comorbid problems. However, we found no evidence that comorbid externalizing and internalizing problems contributed significantly to variations in heart rate levels. With respect to cortisol levels, externalizing but not internalizing problems seemed important contributors. Despite the limited overall sample size in this study, ADHD with and without ODD clinical subgroups were considered. Future research should include different ADHD subgroups, for example related to the clinical presence of depression and anxiety.

Clinical Implications

Taking into account the limited number of studies, the rather patchy and inconsistent results, and the less clear causal inferences, the emerging evidence for circadian effects in ADHD may already have practical value. For example, Harvey et al. (2011) have provided a transdiagnostic approach to treat sleep-wake problems irrespective of the comorbid psychiatric disorders. Such general circadian treatment principles have been suggested to be effective in ADHD: for instance, 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 appears to be 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 & Scates, 2010).

The identification of the afternoon as a period of risk for increased severity of ADHD symptoms (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 behaviour considering its fluctuating expression should be considered. Systematic methods of assessment of time-of-day effects for clinical purposes need to be further developed (Chavez et al., 2009; Pelham et al., 2001; Sonuga-Barke et al., 2004; Swanson et al., 2004). An example of a measure that has become available for use in clinics is the Dundee Difficult Times of Day Scale (DDTODS; Coghill, 2006). Such an instrument may guide the choice for a specific drug-releasing regimen: for example, different methylphenidate preparations have their peak concentration and therefore their peak effect at different times of the day (Sonuga-Barke et al., 2004; Swanson et al., 2004).

Although 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. In chapter 6, findings suggested time-specific deviations in different ADHD subgroups which may provide the initial discussion on the more appropriate timing of specific arousal-based treatments (e.g., stimulant treatment and psychotherapeutic interventions). The finding of nighttime tachycardia in unmedicated children with ADHD (chapter 5) may question the use of stimulant medication that could further increase heart rate levels (Daniels, 2009). This may be an important issue especially for adults with ADHD who are at risk due to higher rates of adult obesity and tobacco use (Cohen et al., 1999; Young & Bray, 2007). As in normal populations, an association between

circadian misalignment and obesity or other cardiovascular risk factors has been reported, which could even further increase health risks in ADHD (Gangwisch, 2009; Scheer et al., 2009).

Challenges for the Future: ADHD as a Function of Context and Time (Part C)

Studies to date provided a fragmented pattern of 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. In particular, the presence of an interaction effect of time-of-day and context should be further explored: several naturalistic studies indeed suggest that the effect of context conditions on ADHD behaviour may vary as a function of time (Antrop, Roeyers, & De Baecke, 2005b; Tsujii et al., 2007).

Theoretical Developments

To address these considerations, we provide a neurobiological working hypothesis (chapter 7) in which 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 & Van der Meere, 1988, 1990). More specifically, we suggest an extension of models of altered arousal mechanisms in ADHD (Sergeant & 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. This model highlights the potential role of the locus coerueleus (LC) disruption in ADHD as a biological mediator of both context specific cognitive energetic effects and context independent circadian effects. This notion was built on two areas of well-established existing evidence, showing that: First, LC and arousal mechanisms are altered in ADHD leading to general difficulties in regulating physiological state in response to changing contextual conditions. Second, LC function, as a key locus in

noradrenergic pathways in the brain, is implicated in arousal more generally and circadian effects specifically.

Future Research Directions

The model described above may serve as a framework for future research on time- and context- dependent behavioural variability in ADHD. First, we described in detail areas for future research exploring the role of LC dysfunction specifically with respect to circadian effects in ADHD. Research suggestions were related to the following predictions (a) LC tonic hyperactivity in ADHD is more expressed at specific times of day than others (evaluation with e.g., fMRI, drug studies); (b) there is a disruption in the circadian rhythms of LC-noradrenergic mediated arousal in ADHD (evaluation with e.g., P3-ERP, pupillometry, EEG); (c) subjects with ADHD show specific alterations in behavioural (e.g., activity and performance) and physiological (e.g., heart rate) measures as a function of time-of-day; and (d) circadian disruptions in LC activity, arousal, and behavioural/ physiological measures will be correlated in ADHD ('combined' research protocol). Though laboratory conditions are compulsory to gain more insight in neurobiological process that underpin ADHD and its variable expression, we pointed at the added value of behavioural and physiological assessments when striving for ecological validity and generalisability.

Secondly, to further explore to what extent specific times of day (especially afternoon; chapter 5) and contextual conditions (e.g., high cognitive, self-regulatory demands; chapter 2 and 3) may interact, we recommend longer-term evaluations of ADHD behaviour (both quantitative and qualitative) in different contexts or under different environmental conditions. We here 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 behaviour and additional measures (e.g., heart rate, saliva cortisol sampling) under different context conditions (e.g., academic tasks, free play) controlling for possible time-of-day effects. Although such protocols commonly 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 behaviour 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).

Finally, considering the heterogeneous nature of ADHD, it is necessary to determine whether circadian- and context-dependent variability in ADHD behaviour and arousal measures is specific for some cases with the disorder. Therefore, we suggested 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, conduct disorder (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. We expect that separate ADHD subgroups may be differentially affected by context and time-of-day effects.

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9

Conclusion

ADHD is one of the most prevalent, high impact psychiatric disorders in children and adolescents. This developmental disorder is characterized by persistent and pervasive attention problems, hyperactivity, and impulsivity symptoms and impairment. Despite significant developments in our knowledge of the pathophysiology of the condition, there are still few examples of therapeutic and clinical innovation that build directly on these advances. This is in part due to limitations in our understanding of the significance of these (laboratory-based) deficits for everyday behaviour and functioning. One finding from the laboratory that may have more practical resonance than others relates to evidence that behavioural symptoms fluctuate both over time and according to different environmental factors. For the purpose of this dissertation, we observed children with and without ADHD in their naturalistic school and home environment to evaluate the fluctuating expression of problems in behaviour regulation and arousal modulation as a function of environmental conditions (*situational variability*) and time of day (*circadian variability*) (for an outline of this dissertation, see chapter 1).

With respect to *situational variability*, the studies included in this dissertation supported differential effects of classroom conditions on the expression of ADHD behaviour. Firstly, our findings highlighted the differential susceptibility of ADHD elementary school aged children to idle time in the classroom. Despite the fact that classroom idle time had a significant effect eliciting more potentially disruptive behaviours in all children, for hyperactivity and noisiness, these effects were more pronounced in children with ADHD as compared to their typically developing classmates (chapter 2). Secondly, similar results were obtained when assessing task-related attention as a function of different instructional conditions: Though children with ADHD were overall less attentive than their peers, group

differences were particularly clear during whole group teaching, individual work, and instructional transition periods, and on highly academic tasks. High self-regulation, information-processing, and motivational demands within these contexts interact with the specific deficits associated with ADHD. These effects persisted even after controlling for the higher levels of teacher supervision observed for ADHD pupils across all contexts (chapter 3).

With respect to *circadian variability*, the literature to date provides initial evidence for differential diurnal arousal patterns in ADHD (for an overview see chapter 4). There are however no studies that use longer term-evaluations of arousal-related measures in ADHD. Using this methodology (evaluations over 5 days), studies in this dissertation supported the presence of time-of-day effects in ADHD. Firstly, 24-hour heart rate registrations revealed an autonomic imbalance with overall higher heart rate levels in our sample of non-medicated children with ADHD as compared to their peers. However, group differences were particularly expressed during night and afternoon hours; a finding independent from activity levels or comorbid psychiatric problems (chapter 5). Secondly, also with respect to diurnal cortisol, we observed a significant interaction between diagnostic group and time. This finding was based on time-specific cortisol deviations in ADHD subgroups: The ADHD without ODD subgroup was relatively hypo-aroused in the morning but hyperaroused in the evening, while the ADHD with ODD subgroup was relatively hyperaroused in the morning and hypo-aroused in the evening (chapter 6).

Despite current study limitations (e.g., confounding factors, sample size), the finding of context- and time- dependent fluctuations in problem behaviour -as observed in children with ADHD in their daily school and home environment- has important clinical implications. For example, classroom interventions might consider targeting specifically these "triggering" periods. They could qualitatively increase their individual teacher supervision levels during these conditions, use supplementary tasks as an alternative for idle time, structure transition periods, use alternative strategies such as small interactive group work, and schedule high academic tasks in the morning. Identifying the afternoon as a period of risk for ADHD may encourage further adjustment of dosing and timing of ADHD medication to optimally treat problematic behaviour considering its fluctuating expression (e.g., different drug-release preparations). As arousal levels are often the target of focus for interventions, knowledge on time-of-day effects in arousal dysregulation may guide specific therapeutic choices for

individual patients (e.g., stimulant treatment and psychotherapeutic interventions); or influence the timing of these interventions, for example related to different ADHD subgroups showing time-specific arousal deviations.

Until now, the specific mechanisms that underpin time-of-day effects in arousal dysregulation are unknown. In this dissertation, we additionally provided a neurobiological working hypothesis that could serve as the basis for future research (chapter 7). This model is an extension of current state-regulation deficit theories and highlights the potential role of locus coeruleus disruption as a biological mediator of both context- and circadian effects. Further insight into the source of variability in behaviour and –relatedly- arousal provides an essential key to the understanding of ADHD. Such knowledge has high practical significance for everyday functioning of children with ADHD and offers the potential to be translated into (context- and time-) specific interventions that are expected to improve academic performance, socio-emotional well-being and long-term outcomes in children with ADHD.

10

Samenvatting

ADHD is één van de meest frequent voorkomende psychiatrische aandoeningen bij kinderen met een belangrijke impact op hun dagdagelijkse functioneren. Deze ontwikkelingsstoornis wordt gekenmerkt door persisterende en pervasieve aandachtsproblemen, hyperactiviteit- en impulsiviteitssymptomen, dewelke belangrijke beperkingen in het functioneren impliceren. Ondanks belangrijke ontwikkelingen inzake de pathofysiologie van deze stoornis zijn de therapeutische en klinische innovaties, die rechtstreeks gelinkt zijn aan deze vorderingen, beperkt. Dit lijkt deels te wijten aan het onvoldoende begrijpen van *op welke manier* onderzoeksbevindingen in een laboratoriumcontext belangrijk zijn voor het alledaags handelen en functioneren. Eén van deze laboratoriumbevindingen, met mogelijk een fundamentele weerklank voor de dagelijkse praktijk, heeft te maken met het feit dat gedrag bij kinderen met ADHD substantieel varieert van setting tot setting en van moment tot moment. In voorliggend proefschrift werd de invloed van *omgevingsfactoren* en *tijdskenmerken* op gedragsregulatie en arousalmodulatie bij kinderen met ADHD in hun natuurlijke school- en thuisomgeving onderzocht (zie hoofdstuk 1 voor een overzicht).

In het eerste deel werd nagegaan in hoeverre ADHD-gedrag varieert in functie van *omgevingsfactoren*. Studies in dit proefschrift bevestigen dat verschillende klascondities (in concreto: *idle time* en educatieve context) bij kinderen met ADHD een andere impact hebben op storend gedrag en op taak-gerelateerde aandacht dan bij hun klasgenoten zonder ADHD. Ondanks het feit dat beide groepen kinderen vaker storend gedrag toonden tijdens wachtsituaties, waren deze contexteffecten met betrekking tot hyperactiviteit en luidruchtigheid significant meer uitgesproken voor kinderen met ADHD dan voor hun klasgenoten (hoofdstuk 2). Hoofdstuk 3 toont vergelijkbare resultaten met betrekking tot

taak-gerelateerde aandacht: Hoewel kinderen met ADHD algemeen meer aandachtsproblemen hadden dan hun leeftijdsgenoten werden groepsverschillen in het bijzonder duidelijk onder specifieke condities: klassikale en individuele werkvormen, sterk academisch georiënteerde taken en periodes met transities/instructies tussen verschillende lessen. In deze condities lijken hoge eisen met betrekking tot zelfregulatie, informatieverwerking en motivatie te interageren met specifiek aan ADHD-gerelateerde problemen. Zelfs met extra steun van leerkrachten aan kinderen met ADHD bleven deze moeilijkheden bestaan.

In het tweede deel van dit proefschrift werden fluctuaties in arousal bekeken als een functie van *tijdskenmerken*. De beschikbare literatuur (zie hoofdstuk 4 voor een overzicht) suggereert een verstoord diurnaal arousal patroon in ADHD. Om deze tijdseffecten beter te begrijpen, hebben we bij kinderen met en kinderen zonder ADHD diurnale patronen in hartfrequentie en cortisol gemeten over een langere tijdsspanne (5 dagen). Onze resultaten wijzen erop dat kinderen met ADHD (zonder medicamenteuze behandeling) een hogere hartfrequentie hebben dan hun leeftijdsgenoten, een bevinding die in het bijzonder tot uiting kwam tijdens de nacht- en namiddaguren. Dit resultaat was niet te verklaren door verhoogde activiteitniveaus en de aanwezigheid van comorbide psychiatrische problemen in deze groep (hoofdstuk 5). Ook wat cortisol betreft werd een significante interactie vastgesteld tussen diagnostische groep en tijd. Deze bevinding was gebaseerd tijd-specifieke afwijkingen in ADHD subgroepen: Kinderen met ADHD zonder ODD waren relatief *hypo-aroused* 's ochtend en *hyperaroused* 's avonds, terwijl kinderen met ADHD én ODD relatief *hyperaroused* waren 's ochtends en *hypo-aroused* 's avonds (hoofdstuk 6).

Ondanks de huidige methodologische beperkingen, heeft de observatie van context- en tijdsgerelateerde fluctuaties in probleemgedrag belangrijke implicaties voor het alledaags functioneren van kinderen met ADHD in hun dagelijkse school- en thuisomgeving. Klasinterventies zouden er bijvoorbeeld naar kunnen streven om specifiek de "uitlokkende" condities van probleemgedrag aan te pakken. Leerkrachten kunnen hun individuele supervisie kwalitatief verhogen tijdens deze specifieke condities, vervangtaken gebruiken als een alternatief voor periodes zonder taak, transitieperiodes structureren, alternatieve lesstrategieën gebruiken zoals interactief werken in kleinere groepjes en sterk academisch georiënteerde taken 's ochtends plannen. Het identificeren van de namiddag als een

risicomoment voor kinderen met ADHD zou verdere aanpassingen van de dosering en timing van ADHD medicatie kunnen stimuleren om zo probleemgedrag optimaal te behandelen, rekening houdend met de fluctuerende expressie van ADHD symptomen (vb. verschillende *drug-release* preparaten). Gezien arousal niveaus vaak de focus van behandeling zijn, kan kennis inzake circadiane effecten in arousal disregulatie leiden tot specifieke therapeutische keuzes voor de individuele patiënt (vb. stimulantia vs psychotherapeutische interventies); of de timing van deze interventies aanpassen in functie van verschillende ADHD subgroepen die tijd-specifieke arousal afwijkingen vertonen.

Tot op heden zijn de specifieke mechanismen die aan de basis liggen van circadiane effecten in arousal disregulatie (nog) niet gekend. In dit proefschrift stellen we bijkomend een neurobiologische werkhypothese voor die de basis kan vormen voor verder onderzoek (hoofdstuk 7). Dit model is een uitbreiding op de huidige state-regulation deficit theorieën en benadrukt de potentiële rol van de locus coeruleus verstoring als een biologische mediator voor zowel context- als circadiane effecten. Verder onderzoek naar de bron van variabiliteit en –gerelateerd- arousal is essentieel om ADHD beter te begrijpen. Kennis inzake context- en tijdsgerelateerde fluctuaties heeft een belangrijke praktische relevantie gezien het potentieel om vertaald te worden naar (context- en tijd-) specifieke interventies waarvan verwacht wordt dat ze de academische prestatie, het socio-emotioneel welzijn en lange termijn uitkomsten verbeteren bij kinderen met ADHD.

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Thanks to ...

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Ring the bells that still can ring
Forget your perfect offering
There is a crack in everything
That's how the light gets in.

L. Cohen

12

Curriculum Vitae

Personalia

Name, Full name:	Lindita Imeraj
Date and place of birth:	11th of March 1982, Jette
Sex:	female
Nationality:	Belgian
E-mail:	lindita_imeraj@hotmail.com

Education and work experience

2007-until now   Training in child and adolescent psychiatry

2011-until now   *Clinical training*: Department of Psychiatry, eating disorders, University Hospital Ghent

2007-2011   *Research training (*PhD student): Behavioural fluctuations in children with ADHD, Ghent University: Faculty of Medicine and Health Sciences, Department of Psychiatry and Medical Psychology

2008-2010   *Courses organized by the Doctoral Schools*, Ghent University

Courses on Statistics: Analyses of Variance, multiple linear regression, longitudinal analyses

Advanced Academic English Writing Skills - Conference Skills

Project Management - Personal Efficiency

Research quality skills

2008 – 2010   *Interuniversity theoretical education child and adolescent psychiatry*

Curriculum Vitae

2000-2007   Ghent University, Medicine, great distinction

            2005   *Thesis:* Het verband tussen endometriose en pre-eclampsie: een case controle studie; Hamerlynck T., Imeraj L.; promotor: Prof. dr. De Sutter

            2004   *Postgraduate education*: Beginselen der Elektrocardiografie

1994-2000   Secondary school: Latin-Mathematics, Heilig Hartcollege, Ganshoren

Publications in international journals (A1)

Imeraj, L., Antrop, I., Roeyers, H., Deschepper, E., Bal, S., and Deboutte, D., 2011. Diurnal variations in arousal: a naturalistic heart rate study in children with ADHD. Eur. Child Adolesc. Psychiatry 20, 381-392. *Awarded with the "ECAP ADHD-Paper of the Year 2011"*

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International presentations

- Oral presentation: Circadian and environmental factors in ADHD (Imeraj L.). BATSA meeting, Ghent, Jan 2011.

- Oral presentation: Influence of peer interactions and teacher supervision on behavioural fluctuations in children with ADHD (Imeraj L., Antrop I., Deboutte D., Roeyers H.). EABCT congress, Milan, October 2010.

- Oral presentation: Are circadian factors different in children with ADHD? A naturalistic approach (Imeraj L., Antrop I., Deboutte D., Roeyers H.). IACAPAP Congress, Beijing, June 2010.

- Poster presentation: 24-hour heart rate patterns in children with ADHD: a naturalistic approach (Imeraj L., Antrop I., Deboutte D., Roeyers H.). Eunethydis, Amsterdam, May 2010.

- Poster presentation *(+ poster price)*: Role of circadian rhythms in ADHD and behavioral fluctuations (Imeraj L., Antrop I., Deboutte D., Roeyers H.). International Congress of ADHD, Vienna, May 2009.

- Poster presentation: Fluctuations in ADHD symptomatology: influence of circadian factors (Imeraj L., Antrop I., Deboutte D., Roeyers H.). Eunethydis, Manheimm, October 2008.

National presentations

- Oral presentation: Contextspecificiteit van ADHD gedrag in de klasomgeving (Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams congres kinder- en jeugdpsychiatrie, Leuven, September 2011.

- Poster presentation *(+ poster price)*: Kwantiteit en kwaliteit van leerkrachtmonitoring bij kinderen met ADHD (Moreaux E., Delbare F., Imeraj L., Antrop I., Roeyers H., Deboutte D.). Vlaams congres kinder- en jeugdpsychiatrie, Leuven, September 2011.

- Workshop: Invloed van contextfactoren en circadiane kenmerken in gedragsfluctuaties bij kinderen met ADHD (Imeraj L., Antrop I.). SIG, Destelbergen, November 2010.

- Oral presentation: Circadiaanse kenmerken bij kinderen en jongeren met ADHD (Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams Congres Geestelijke Gezondheidszorg, Ghent, September 2010.

- Oral presentation: Rol van circadiaanse ritmes in ADHD en gedragsschommelingen (Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams Congres Kinder-en jeugdpsychiatrie, Ghent, September 2009.

- Poster presentation *(+ poster prize)*: Invloed van circadiaanse factoren bij kinderen met ADHD (Tilley J., Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams Congres Kinder-en jeugdpsychiatrie, Ghent, September 2009.

- Poster presentation: Invloed van speeltijd op het gedrag van kinderen met ADHD (Smet F., Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams Congres Kinder-en jeugdpsychiatrie, Ghent, September 2009.

- Poster presentation: Geslachtsverschillen bij kinderen met ADHD: observatie in de natuurlijke klasomgeving (de Vries E., Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams Congres Kinder-en jeugdpsychiatrie, Ghent, September 2009.

- Oral presentation: Rol van circadiaanse ritmes in ADHD en gedragsschommelingen (Imeraj L.). Vlaamse Vereniging Assistenten Psychiatrie, Grimbergen, September 2009.

- Oral presentation: Gedragsschommelingen bij kinderen met ADHD: Contextuele en circadiane invloeden (Imeraj L., Antrop I.). Symposium Kinder- en jeugdpsychiatrie UZ Ghent - Brussels, Ghent, May 2008.

- Oral presentation: Observatiestudies tonen fluctuaties in en contextuele invloeden op gedrag van kinderen met ADHD (Imeraj L., Antrop I., Deboutte D., Roeyers H.). Vlaams Congres Kinder-en jeugdpsychiatrie, Brussels, February 2008.

Supporting theses at master level

- Sofie Van Den Abeele (2012): Slaap-waak ritmes bij kinderen met ADHD: Subjectieve en objectieve evaluatie
- Liesbeth Cuykens (2012): *Evening preference* bij adolescenten: Associatie met ADHD symptomatologie
- Femke Delbaere & Eline Moreaux (2011): Leerkracht supervisie en monitoring bij kinderen met ADHD
- Sarah Bosma (2011): Spel- en klasgedrag bij kinderen met ADHD: een natuurlijke observatie
- Jehanne Leuwers (2010): Invloed van lescontext en klasstructuur bij kinderen met ADHD
- Celien De Vlaminck (2010): Delay aversion bij kinderen met ADHD: een ecologisch valide studie
- Lize Verbeke (2010): Micro-omgeving bij kinderen met ADHD: sociale interactie met peers en monitoring door de leerkracht
- Jessica Tilley (2009): Invloed van circadiaanse factoren bij kinderen met ADHD
- Elsbeth de Vries (2009): Geslachtsverschillen bij kinderen met ADHD: observatie in de natuurlijke klasomgeving
- Frederick Smet (2009): Invloed van speeltijd op het gedrag van kinderen met ADHD

13

Abbreviation List

ADHD	attention-deficit hyperactivity disorder
ANOVA	analysis of variance
APA	American psychiatric association
AUC	area under curve
BMI	body mass index
CAN	central autonomic network
CBCL	child behaviour checklist
CD	conduct disorder
CLOCK gene	circadian locomotor output cycles kaput gene
CRF	corticotropin releasing factor
DBDRS	disruptive behaviour disorder rating scale
DLMO	dim light melatonin onset
DMH	dorsomedial hypothalamic nucleus
DRD-4 gene	dopamine receptor D_4 gene
DSM-IV	diagnostic and statistical manual of mental disorders, 4th edition
ECG	electrocardiogram
EEG	electroencephalogram
EF	executive function
ERP	event related potential
ES	effect size
fMRI	functional magnetic resonance imaging

Abbreviations

GEE	generalized estimation equation
GR	glucocorticoid receptors
GUCCI	Ghent University classroom coding inventory
HC	hippocampus
HPA axis	hypothalamic-pituitary-adrenal axis
LC	locus coeruleus
MEQ	morningness-eveningness questionnaire
MR	mineralocorticoid receptors
MSLT	multiple sleep latency test
NE	noradrenaline
ODD	oppositional defiant disorder
P-DISC-IV	diagnostic interview schedule for children, parent version 4
PET	positron emission tomography
PFC	prefrontal cortex
PSG	polysomnography
RAS	reticular activation system
RIA	radioimmuno assay
SCN	suprachiasmatic nucleus
SES	socio-economic status
SOI	sleep onset insomnia
TRF	teacher report form
VLPO area	sleep-related ventrolateral preoptic area
WISC-III-R	Wechsler intelligence scale for children, version 3 revised

Notes

Notes