Sleep in Adults with Attention-Deficit/Hyperactivity Disorder of the Predominantly Inattentive and Combined Subtypes

by

Sun Young Rosalia Yoon

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
Institute of Medical Science
University of Toronto

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Doctor of Philosophy
Institute of Medical Science
University of Toronto
2015

Abstract

Subjective and objective data on correlates of sleep were collected from adults with Attention-Deficit/Hyperactivity Disorder (ADHD) to determine whether ADHD of the Predominantly Inattentive (ADHD-I) and Combined (ADHD-C) subtypes differ with respect to the nature, prevalence, and impact of sleep disturbances on the core symptoms of ADHD.

Subjective data were collected from 45 ADHD-I (mean 40 ± 11 years, 24% female) and 81 ADHD-C (mean 37 ± 10 years, 27% female) adults. A high proportion of ADHD subjects had complaints of excessive daytime sleepiness, poor sleep quality and fatigue. Sleep quality and fatigue were worse for ADHD-I than for ADHD-C subjects. The interrelationships between daytime sleepiness, sleep quality, and fatigue also differed between ADHD subtypes, suggesting differences in the interplay of sleep and wakefulness in ADHD-I and ADHD-C.

The idea that the interplay of sleep and wakefulness differs in ADHD subtypes was further supported by findings associated with objective measures of sleep in 27 ADHD-I (mean 39 ± 12 years, 33% females) and 41 ADHD-C (mean 37 ± 9 years, 20% females) adults. Specifically, dim light melatonin onset (DLMO) time was found to be associated with inattention in ADHD-I,
and with hyperactivity/impulsivity in ADHD-C. Regarding polysomnography (PSG) measures of sleep, symptoms of inattention were found to be associated with respiratory-event related arousals (RERA) in ADHD-I, and symptoms of hyperactivity/impulsivity were found to be associated with correlates of REM sleep in ADHD-C. These findings suggest a differential role of circadian cycles and sleep in the neuromodulation of the core symptoms of ADHD in ADHD subtypes.

Taken together, the findings suggest that ADHD subtype differences extend to the realm of sleep. Importantly, subtype differences lie, not in measures of sleep *per se*, but rather in the interrelationships between measures of sleep and the core symptoms of ADHD, suggesting ADHD-subtype differences in the interplay of sleep and wakefulness.
This dissertation is an original intellectual product of the author, Sun Young Rosalia Yoon.

I was responsible for the collection of all subjective data and some objective data. The bulk of objective data were collected and provided by the sleep technicians at the Toronto Sleep and Alertness Clinic, and for this, I am immensely grateful. I was responsible for all aspects of data analysis, as well as manuscript composition, under the supervision of Dr Colin Shapiro.

Portions of the text in Section 1.1, Section 1.4 and its subsections, and Tables 1.4 to 1.7 have been published [Yoon SY, Jain U, Shapiro C (2012) Sleep in attention-deficit/hyperactivity disorder in children and adults: past, present and future. Sleep Med Rev 16: 371-388]. I was the first author of this article, and I was responsible for all major areas of concept formation and manuscript composition. Jain U and Shapiro C were supervisory authors and were involved in manuscript edits.

Portions of the text in Section 1.3.3 and its subsections, and Figures 1.4 and 1.7 have been published [Yoon SYR & Shapiro CM (2013) Chronobiology of Sleep – Circadian Rhythms, Behavior, and Performance. In: Kushida C. (ed.) The Encyclopedia of Sleep, vol. 1, pp. 426-434. Waltham, MA: Academic Press]. I was the first author of this chapter, and I was responsible for all major areas of concept formation and manuscript composition. Shapiro CM was the supervisory author and he was involved in manuscript edits.

Tables 2.2, 3.1 to 3.7, and 4.1; Figure 4.1; and portions of the text in Section 3.1.2 and its subsections, and Section 4.1.2 and its subsections have been published [Yoon SYR, Jain U, Shapiro C (2013) Sleep and daytime function in adults with attention-deficit/hyperactivity disorder: subtype differences. Sleep Med 14: 648-655]. I was the first author of this article and I was responsible for all major areas of concept formation and manuscript composition. Jain U and Shapiro C were supervisory authors and were involved in manuscript edits.

Tables 3.13 to 3.15, 4.4, and 4.5; and portions of the text in Section 3.2.2 and its subsections, and Section 4.2.2 and its subsections are part of a manuscript that has been submitted – but not yet...
accepted – for publication to *Sleep* [Yoon SYR, Jain U, Shapiro C (2014) Objective measures of sleep and the core symptoms of attention-deficit/hyperactivity disorder in adults: subtype differences]. I was the first author of this manuscript and I was responsible for all major areas of concept formation and manuscript composition. Shapiro C was the supervisory author and he was involved in manuscript edits.

Tables 3.8 to 3.12; and portions of the text in Section 3.2.1 and its subsections, and Section 4.2.1 and its subsections are part of a manuscript that will be submitted to Sleep Medicine [Yoon SYR, Jain U, Shapiro C (2014) Chronotype and attention-deficit/hyperactivity disorder (ADHD) – relationships between circadian preference, melatonin, and the core symptoms of ADHD in the Inattentive and Combined subtypes of ADHD]. Shapiro C was the supervisory author and he was involved in manuscript edits.

Table 3.1 and portions of the text in Appendix VII are part of a manuscript that has not been submitted. [Yoon SYR, Jain U, Shapiro C (2014) Personality traits and symptoms profiles among adults with Attention-Deficit/Hyperactivity Disorder of the Predominantly Inattentive and Combined Subtypes].
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Last but not least, I would like to express my immense gratitude to all the study subjects who volunteered their time and energy to make this project possible.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine (serotonin)</td>
</tr>
<tr>
<td>5-HTP</td>
<td>5-hydroxytryptophan</td>
</tr>
<tr>
<td>5-HTT</td>
<td>serotonin transporter gene</td>
</tr>
<tr>
<td>6R</td>
<td>6-repeat allele</td>
</tr>
<tr>
<td>7R</td>
<td>7-repeat allele</td>
</tr>
<tr>
<td>10R</td>
<td>10-repeat allele</td>
</tr>
<tr>
<td>A1R</td>
<td>adenosine receptor 1</td>
</tr>
<tr>
<td>AAAD</td>
<td>aromatic amino acid decarboxylase</td>
</tr>
<tr>
<td>AANAT</td>
<td>arylalkylamine N-acetylamine N-acetyltransferase</td>
</tr>
<tr>
<td>ACC</td>
<td>anterior cingulate cortex</td>
</tr>
<tr>
<td>Ach</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>AD</td>
<td>adenosine</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention-deficit/hyperactivity disorder</td>
</tr>
<tr>
<td>ADHD-I</td>
<td>attention-deficit/hyperactivity disorder predominantly inattentive subtype</td>
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<tr>
<td>ADHD-C</td>
<td>attention-deficit/hyperactivity disorder predominantly combined subtype</td>
</tr>
<tr>
<td>ADHD-H/I</td>
<td>attention-deficit/hyperactivity disorder predominantly hyperactive-impulsive subtype</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>AHA</td>
<td>apnea-hypopnea arousal index</td>
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<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
</tr>
<tr>
<td>AI</td>
<td>arousal index</td>
</tr>
<tr>
<td>AM</td>
<td>morning chronotype</td>
</tr>
<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of co-variance</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>AR</td>
<td>adenosine receptor</td>
</tr>
<tr>
<td>AR₁</td>
<td>adenosine receptor type 1</td>
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<tr>
<td>AR₂</td>
<td>adenosine receptor type 2</td>
</tr>
<tr>
<td>ARAS</td>
<td>ascending reticular activating system</td>
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ASRS  adult ADHD self-report scale
ATP  adenosine triphosphate
ATX  atomoxetine
BADDs  Brown’s attention deficit disorder scale
BCE  before the common era
BD  bipolar disorder
BF  basal forebrain
BMAL1  brain and muscle ARNT-like 1
BMI  body mass index
CAARS  Conner’s adult ADHD rating scale
CAARS-S:L  Conner’s adult ADHD rating scale – self-report: long version
CAMH  Centre for Addiction and Mental Health
cAMP  cyclic adenosine monophosphate
CAP  cyclic alternating pattern
CBT  core body temperature
CCG  clock-controlled gene
CD  conduct disorder
CHRNA4  neuronal acetylcholine receptor subunit α4 gene
CLOCK  circadian locomotor output cycles kaput
COMT  catechol-O-methyl transferase
Cry  cryptochrome
CSA  central sleep apnea
CSM  composite scale of morningness
CT  circadian time
D1-D5  dopamine receptor subtypes D1 to D5
DA  dopamine
DAT  dopamine transporter
DAT1  dopamine transporter gene
DEX  dextroamphetamine
DLMOff  dim light melatonin offset
DLMO  dim light melatonin onset
DRD4  dopamine D4 receptor gene
DRD5 dopamine D₅ receptor gene
dRN dorsal raphe nuclei
DSM Diagnostic and Statistical Manual of Mental Disorders
DSPS delayed sleep phase syndrome
DTI diffusion tensor imaging
ECG electrocardiography
EDS excessive daytime sleepiness
EEG electroencephalography
ELISA enzyme-linked immunosorbent assay
EMG electromyography
EOG electro-oculography
ESS Epworth sleepiness scale
fMRI functional magnetic resonance
FSS fatigue severity scale
G guanine
GABA gamma-aminobutyric acid
GAD generalized anxiety disorder
GHRH growth hormone releasing hormone
GHT geniculohypothalamic tract
GI gyrification index
Glu glutamate
Gs Gₛ alpha protein
HCN cAMP-modulated cation channel
HIOMT hydroxyindole-O-methyltransferase
HTR1B serotonin receptor gene
Hz hertz
I intermediate chronotype
IGL intergeniculate leaflet
Ih hyperpolarization-activated cation currents
IH idiopathic hypersomnia
IL-1β interleukin-1 beta
LC locus coeruleus
<table>
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<tr>
<th>Acronym</th>
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<tr>
<td>LD</td>
<td>learning disorder</td>
</tr>
<tr>
<td>LDT</td>
<td>laterodorsal tegmental nuclei</td>
</tr>
<tr>
<td>LH</td>
<td>lateral hypothalamus</td>
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<td>MANCOVA</td>
<td>multiple analysis of co-variance</td>
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<td>MANOVA</td>
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<td>MDD</td>
<td>major depressive disorder</td>
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<td>MEQ</td>
<td>Horne-Ostberg morningness-eveningness questionnaire</td>
</tr>
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<td>mRN</td>
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<tr>
<td>MPH</td>
<td>methylphenidate</td>
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<td>MSLT</td>
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<td>multiple wakefulness test</td>
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<td>NE</td>
<td>norepinephrine</td>
</tr>
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<td>protein kinase A</td>
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<td>PLMA</td>
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<td>periodic limb movement index</td>
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<td>PLMS</td>
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<tr>
<td>PM</td>
<td>evening chronotype</td>
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</tr>
<tr>
<td>PPT</td>
<td>pedunculopontine nuclei</td>
</tr>
<tr>
<td>PRF</td>
<td>pontine reticular formation</td>
</tr>
<tr>
<td>Process C</td>
<td>endogenous circadian process</td>
</tr>
<tr>
<td>Process S</td>
<td>homeostatic process</td>
</tr>
<tr>
<td>PS</td>
<td>primary snoring</td>
</tr>
<tr>
<td>PSG</td>
<td>polysomnography</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburgh sleep quality index</td>
</tr>
<tr>
<td>PTSD</td>
<td>post-traumatic stress disorder</td>
</tr>
<tr>
<td>PVN</td>
<td>paraventricular nucleus</td>
</tr>
<tr>
<td>RDI</td>
<td>respiratory disturbance index</td>
</tr>
<tr>
<td>REM</td>
<td>rapid eye movement</td>
</tr>
<tr>
<td>REML</td>
<td>rapid eye movement sleep latency</td>
</tr>
<tr>
<td>RERA</td>
<td>respiratory event related arousal index</td>
</tr>
<tr>
<td>RGC</td>
<td>retinal ganglionic cell</td>
</tr>
<tr>
<td>RHT</td>
<td>retinohypothalamic tract</td>
</tr>
<tr>
<td>RLS</td>
<td>restless legs syndrome</td>
</tr>
<tr>
<td>RN</td>
<td>raphe nuclei</td>
</tr>
<tr>
<td>SAI</td>
<td>spontaneous arousal index</td>
</tr>
<tr>
<td>SCID</td>
<td>structured clinical interview for DSM-IV axis I disorders</td>
</tr>
<tr>
<td>SCN</td>
<td>suprachiasmatic nuclei</td>
</tr>
<tr>
<td>SDB</td>
<td>sleep disordered breathing</td>
</tr>
<tr>
<td>SE</td>
<td>sleep efficiency</td>
</tr>
<tr>
<td>SN</td>
<td>substantia nigra</td>
</tr>
<tr>
<td>SNAP25</td>
<td>synaptosomal associated protein oh 25 kD gene</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>SOL</td>
<td>sleep onset latency</td>
</tr>
<tr>
<td>SOT</td>
<td>sleep onset time</td>
</tr>
<tr>
<td>SWS</td>
<td>slow wave sleep</td>
</tr>
<tr>
<td>T</td>
<td>thymine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>TCI</td>
<td>temperament and character inventory</td>
</tr>
<tr>
<td>TH</td>
<td>tryptophan hydroxylase</td>
</tr>
<tr>
<td>TMN</td>
<td>tuberomammillary nucleus</td>
</tr>
<tr>
<td>TNFα</td>
<td>tumor necrosis factor alpha</td>
</tr>
<tr>
<td>TSP</td>
<td>total sleep period</td>
</tr>
<tr>
<td>TST</td>
<td>total sleep time</td>
</tr>
<tr>
<td>UARS</td>
<td>upper airway resistance syndrome</td>
</tr>
<tr>
<td>UTR</td>
<td>untranslated region</td>
</tr>
<tr>
<td>VLPO</td>
<td>ventrolateral preoptic nucleus</td>
</tr>
<tr>
<td>VBM</td>
<td>voxel-based morphometry</td>
</tr>
<tr>
<td>VMH</td>
<td>ventromedial hypothalamic nucleus</td>
</tr>
<tr>
<td>VNTR</td>
<td>variable number of tandem repeats</td>
</tr>
<tr>
<td>vPAG</td>
<td>ventral periaqueductal grey matter</td>
</tr>
<tr>
<td>VTA</td>
<td>ventral tegmental area</td>
</tr>
<tr>
<td>WFIRS-S</td>
<td>Weiss functional impairment rating scale – self report</td>
</tr>
<tr>
<td>WFIRS-P</td>
<td>Weiss functional impairment rating scale – parent report</td>
</tr>
<tr>
<td>WRAADS</td>
<td>Wender-Reimherr adult ADD scale</td>
</tr>
<tr>
<td>WSR</td>
<td>Weiss symptom record</td>
</tr>
</tbody>
</table>
Chapter 1
INTRODUCTION

1.1 Preamble

Attention-deficit/hyperactivity disorder (ADHD) is a chronic and highly heritable psychiatric condition characterized by the core symptoms of inattention, impulsivity, and hyperactivity which first manifest in infancy (APAS, 2000). Estimated to affect 5% of children worldwide, ADHD is one of the most common psychiatric disorders in childhood (Polanczyk et al., 2007).

Accounts of ADHD date back to the early 1900’s, when the disorder was not yet well defined and conditions such as ADHD, conduct disorders (CD), and oppositional defiant disorder (ODD) were clumped together under the rubric of “moral imbecility”, in which individuals were described as having an “…inability to display moral restraint and lawful behaviour (while) … being, in many cases, of normal or even superior intelligence…” (Rafalovich, 2004).

Since then, considerable research has been conducted. Traditionally thought of as a condition exclusively associated with childhood, evidence from longitudinal studies over the past two decades points to ADHD as a pervasive condition that continues with some robustness into adulthood in over 60% of patients (Weiss et al., 1985; Barkley et al., 1990; Mannuzza et al., 1991; Faraone et al., 2000a; Spencer et al., 2007). With the advent of neuroimaging techniques and advances in the field of neuropsychopharmacology, it is now understood that ADHD is primarily associated with abnormalities in areas of the brain involved with catecholamine signaling (Arnsten, 2006; Curatolo et al., 2009). Moreover, recent studies indicate that serotonergic and cholinergic pathways may also be affected (Potter et al., 2006; Muller et al., 2008), suggesting an intricate interplay of signaling pathways in the pathology of ADHD.

With a growing public recognition of adult ADHD, unprecedented numbers of adults are now seeking evaluation, diagnosis, and treatment of symptoms resembling ADHD. However, ADHD pathology is not fully understood, and first-line treatments for ADHD often do not successfully alleviate the full spectrum of symptoms, and/or are coupled with undesirable side effects that
can lead to non-compliance with treatment (Oades, 2008). Moreover, first-line treatments are not effective in up to 30% of patients (Oades, 2008).

In the United States, ADHD is estimated to affect 4.4% of the working adult population (Kessler et al., 2005) and, if left untreated, ADHD is associated with large social and economic impacts. Subjects with ADHD are prone to procrastination, academic underachievement, poor time management skills, reduced work performance, higher rates of unemployment and driving accidents, significantly lower income, involvement in criminal activity, poor self-image, and difficulty maintaining relationships (Borland & Heckman, 1976; Morrison et al., 1980a; 1980b; Faraone et al., 2000b; Swensen et al., 2004). Subjects with ADHD reportedly make significantly higher use of health, social, and educational services, which in 2000 amounted to an estimated $31.6 billion (Birnbaum et al., 2005; Secnik et al., 2005). Moreover, each year, workers with ADHD are estimated to have on average 8 more days of missed work and 35 more days of reduced work (quantity and/or quality) than workers without ADHD (de Graaf et al., 2008). In 2003, the incremental loss of workplace productivity due to ADHD in the US was estimated to cost between $67 billion and $116 billion (Biederman & Faraone, 2006). In comparison, the economic burden of insomnia was estimated to be $30 billion to $35 billion in 1994 (Chilcott & Shapiro, 1996), and the economic burden of depression was estimated to be $83.1 billion in 2000 (Greenberg et al., 2003). These figures suggest that ADHD is among the leading causes of social and economic burden in western society, highlighting the need for better understanding, recognition, and treatment of ADHD.

While the cumulative research over the past 50 years has contributed significantly to the understanding of ADHD, the etiological factors underlying its pathology are still not well understood. A major roadblock in the understanding of ADHD has been the fact that it is a highly heterogeneous condition for which multiple factors can lead to the ADHD phenotype. Added to this is the fact that ADHD is often co-morbid with psychiatric and/or neurological disorders that can present difficulties in delineating etiological factors exclusively associated with ADHD. The frequency of co-morbidities in ADHD is, in fact, so high that one may wonder about the extent to which such co-morbidities can be separated from ADHD. However, while the presence of co-morbidities poses a challenge in the investigation of ADHD pathology in its pure form, it can also provide valuable information about ADHD in all its forms. The heterogeneity of ADHD in the presentation of symptoms, subtypes, and co-morbidities may be
the phenotypic expression of multiple pathway mechanisms involved in ADHD and, as a result, it may be the key to understanding the different neurological mechanisms underlying ADHD.

The focus of this thesis is on sleep disturbances in adult ADHD. The study of sleep in ADHD is important not only because of the high rates of co-morbidity, as studies indicate that 25-50% of children and more than half of adults with ADHD suffer from sleep problems (Dobson & Zhang, 1999; Gruber et al., 2000; Hvolby et al., 2008); but also because, as discussed in the following sections, some areas of the brain that are affected in ADHD are also involved in the regulation of sleep, suggesting that common mechanisms may underlie the pathologies of sleep disorders and ADHD.

1.2 ADHD

1.2.1 A historical account of ADHD

The recognition that ADHD is a highly heritable, chronic, and treatable psychiatric disorder is relatively new and there are still factions within the public that are skeptical as to its legitimacy, arguing that ADHD is an invention of the 20th century rooted in the pathologization of socially deviant behaviours (Parens & Johnston, 2009). Furthermore, there is a perception that this “entity” is driven by disease-mongering clinicians and pharmaceutical companies hungry for profit – a message that was relayed by Pringle & Rosenberg (2012) in their eloquently titled article “Big Pharma’s newest invention: Adult ADHD”.

Nevertheless, accounts of ADHD-like symptoms date as far back as the end of the 18th century, suggesting that clinical interest in the pathology surrounding ADHD started long before any social constructs of the 20th century or hidden agendas of pharmaceutical companies.

The first known clinical account of a disorder similar to our current understanding of ADHD dates back to 1798, when Sir Alexander Crichton described a condition of “morbid alterations to (...) attention” marked by “the incapacity of attending with a necessary degree of constancy to any one object”, “an unnatural degree of mental restlessness”, and “fidgets” (Crichton, 1798; in Lange et al., 2010). By the beginning of the 1900’s, the concept of ADHD had evolved – and expanded – to include more of the symptoms that are currently recognized to be associated with
ADHD. In what was referred to as “psychical conditions (…) with an abnormal defect of moral control” while “being, in many cases, of normal or even superior intelligence”, Sir George Frederic Still described “lawless children” with a penchant for “immediate gratification”, “a morbid failure to control (…) emotional activities” and “disregard for command and authority” (Still, 1902; Lange et al., 2010) – behaviours which by current standards would be recognized as impulsivity, delay aversion, emotional lability, conduct disorders, and oppositional defiant disorders (Conners 2000; Palmer & Finger, 2001; Barkley 2006; Lange et al., 2010).

Further progress in the characterization and understanding of ADHD took place in the 1920’s and in association with an epidemic of encephalitis lethargica. Also known as von Economo’s encephalitis (in honour of Constantin von Economo – a neurologist who first described the disease in 1917 and who, incidentally, would go on to identify areas of the brain involved in sleep-wake regulation – see section 1.3.3), encephalitis lethargica was a new and strange type of encephalitis first reported in Vienna, that would soon spread to the rest of Europe, North America, and eventually become a worldwide epidemic lasting until 1926 (Dickman, 2001). The epidemic claimed the lives of some 40 million people (Kolata, 2001), and for those who survived, encephalitis lethargica was associated with chronic residual effects that negatively impacted quality of life, as discussed below.

While the epidemic had devastating consequences for the population, the study of encephalitis lethargica pathology proved to be instrumental in establishing for the first time a connection between symptoms of ADHD and brain dysfunction. von Economo identified three types of encephalitis lethargica: the somnolent-ophthalmoplegic form, the amyostatic akinetic form, and the hyperkinetic form (Dickman, 2001; Triarhou, 2006). His examinations of post-mortem brain specimens led him to discover that encephalitis lethargica was marked by inflammatory changes in the basal ganglia, midbrain and pons (Triarhou, 2006). Of relevance to this dissertation, the residual effects associated with the hyperkinetic form of encephalitis lethargica were described as “post-encephalitic hyperkinetic syndrome”, which were said to include common symptoms of ADHD such as hyperactivity, distractibility, irritability, and troublesome sleeplessness (Ross & Ross, 1976; Dickman 2001; Lange et al., 2010). In reviewing the literature on the pathology of encephalitis, Bond & Partridge (1926) concluded that the behavioral changes observed in post-encephalitic children were likely a result of physical changes in the basal ganglia (Baumeister et al., 2012).
The idea that the hyperkinetic symptoms observed in post-encephalitic children were somehow linked to brain damage was further solidified by Kahn & Cohen (1934), who described a syndrome they called “Organic Drivenness”, characterized by an “inner impulsion”, “hyperkinesis”, and “lack of continued concentration” and – based on von Economo’s findings – proposed to stem from damage to the brain stem (Baumeister et al., 2012).

While speculation about the links between brain damage and the behavioral changes in post-encephalitic children was taking place, the conceptualization of ADHD was also becoming more defined. In 1932, German physicians Franz Kramer and Hans Pollnow published a report on a “hyperkinetic disease of infancy” which they described as being characterized by symptoms that were ubiquitously associated with other diseases (such as encephalitis lethargica) but which as a group appeared to constitute a unique and distinguishable condition (Lange et al., 2010). As implied by its name, the most overt characteristic of this hyperkinetic disease of infancy was marked motor activity that appeared to be aimless and which, for most children, diminished with age (Lange et al., 2010). In line with the modern concept of ADHD, other characteristics of this hyperkinetic disease were high distractibility, inability to complete tasks, and difficulty concentrating on complex tasks (Lange et al., 2010).

The idea that hyperactive behavior stemmed from brain damage became increasingly consolidated throughout the 1930s and 1940s (Ross & Ross, 1976; Lange et al., 2010) and eventually led to the conceptualization of the “minimal brain damage” theory. This theory was characterized by the (unfounded) assumption that, since mild damage to the brain in infancy could lead to hyperactivity, hyperactivity in childhood must stem from minimal brain damage – even if this could not be demonstrated (Lange et al., 2010).

Following the criticisms on the flawed reasoning underlying the minimal brain damage theory, the theory was replaced in the 1960s by the minimal brain dysfunction theory, which proposed that hyperkinetic/impulsive children were afflicted by a dysfunction in the diencephalon, based on the observation that these children – irrespective of whether they had a history or evidence of brain injury – exhibited some electroencephalogram (EEG) patterns that distinguished them from healthy controls (Laufer, 1957; Lange et al., 2010). In 1966, minimal brain dysfunction was officially declared to be associated with impairment in the control of attention, impulse, and motor function (Clements, 1966); and in 1968, an early classification of ADHD appeared in the
Table 1.1 Evolution of ADHD across DSM editions

<table>
<thead>
<tr>
<th>DSM Edition</th>
<th>Typology and Subtyping</th>
<th>Conceptualization</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-II</td>
<td>Hyperkinetic Reaction of Childhood</td>
<td>Hyperactivity perceived as the core problem</td>
</tr>
</tbody>
</table>
| DSM-III     | Attention Deficit Disorder (ADD)  
• ADD with hyperactivity (ADD/H)  
• ADD without hyperactivity (ADD/noH) |  
• Inattention and impulsivity – but not hyperactivity – perceived as the core problems.  
• Recognition that the condition could occur with or without hyperactivity.  
• Symptom lists and cut-off scores were introduced for inattention, impulsivity, and hyperactivity. |
| DSM-III-R   | Attention-Deficit Hyperactivity Disorder |  
• ADD/noH no longer recognized as a subtype due to lack of evidence on qualitative difference between ADD/H and ADD/noH.  
• Symptoms of inattention, impulsivity, and hyperactivity were combined into a single list with a single cut-off score. |
| DSM-IV      | Attention-Deficit/hyperactivity disorder  
• ADHD predominantly inattentive  
• ADHD predominantly hyperactive/impulsive  
• ADHD combined |  
• Multi-dimensional conceptualization of ADHD.  
• Inattention and/or hyperactivity/impulsivity perceived as the core problems.  
• Symptom lists and cut-off scores introduced for inattention and hyperactivity/impulsivity. |

Table adapted from Baeyens et al., 2006

Second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) under the label of “Hyperkinetic Reaction of Childhood” (Lange et al., 2010). Thereafter, the classifications and diagnostic criteria for ADHD changed significantly over the course of 3 new editions of the DSM (DSM-III, DSM-III-R, and DSM-IV), reflecting changes in the conceptualization of ADHD, as shown in table 1.1.


Because recruitment of subjects to this study occurred between June 2009 and June 2010 (see Materials and Methods), DSM-IV-TR guidelines were used in this study and, thus, the sections
that follow describe ADHD as defined by the DSM-IV-TR. The implications of the changes introduced in DSM-V are briefly discussed in section 1.2.2.2.

1.2.2 Clinical features of adult ADHD

According to the DSM-IV-TR, there are five essential features of ADHD (APA, 2000):

i. Persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and is more severe than is typically observed in individuals at comparable level of development.

ii. Some hyperactive-impulsive or inattentive symptoms must have been present before seven years of age.

iii. Some impairment from the symptoms must be present in at least two settings.

iv. There must be clear evidence of interference with developmentally appropriate social, academic or occupational functioning.

v. The disturbance does not occur exclusively during the course of Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorders and is not better accounted for by another disorder.

Additionally, the DSM-IV-TR states that ADHD is associated with eighteen impairing symptoms that can be divided into two clusters: symptoms of inattention and symptoms of hyperactivity-impulsivity. Based on the presentation of these symptoms, subjects may be classified as:

i. ADHD Predominantly Inattentive (ADHD-I) Type: When six or more symptoms of inattention, but fewer than six symptoms of hyperactivity-impulsivity have persisted for at least six months.
ii. ADHD Predominantly Hyperactive-Impulsive (ADHD-H/I) Type: When six or more symptoms of hyperactivity-impulsivity, but fewer than six symptoms of inattention have persisted for at least six months.

iii. ADHD Predominantly Combined (ADHD-C) Type: When six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity have persisted for at least six months.

The adult ADHD patient exhibits similar features to the childhood presentation (Wender et al., 1981). However, while the main features of inattention, impulsivity and hyperactivity remain in the adult, the disorder is reported to progress with an internalization of symptoms, such that characteristics of childhood ADHD such as restlessness and fidgetiness may diminish, while problems with inattention become more pronounced with increasing attention-demanding tasks (Biederman et al., 1993; Millstein et al., 1997; Biederman et al., 2000). Due to the internalization of hyperactive and impulsive symptoms, it has been proposed that ADHD-H/I phenotype in childhood is a precursor to the ADHD-C phenotype in adulthood, and that the ADHD-C phenotype in childhood is a precursor to the ADHD-I phenotype in adulthood (Barkley & Murphy, 1998). The end result is that most adults with ADHD fall under the category of either ADHD-I or ADHD-C, though the ADHD-C subtype is more common, representing about two thirds of patients (Lahey et al., 1994).

1.2.2.1 Differences between the Inattentive and Combined subtypes of ADHD

Both Inattentive and Combined subtypes of ADHD are affected by symptoms of inattention. The primary difference between Inattentive and Combined subtypes is that clinically significant hyperactive/impulsive behaviours are only present in ADHD-C patients (APA 2000). Extensive research, however, suggests that differences between ADHD subtypes are not limited to the core symptoms of ADHD, but extend to associated symptoms and co-morbidities, as studies indicate that subjects with ADHD-C are more prone to behavioural and social problems (Wolraich et al., 1996; Gaub & Carlson, 1997; McBurnett et al., 1999); as well as the development of co-morbidities such as anxiety, depression, drug addiction, tic disorders, bipolar disorder (BD), and
externalizing disorders such as ODD and CD than subjects with ADHD-I (Faraone et al., 1998a; b; Lalonde et al., 1998; Willcutt et al., 1999; Saules et al., 2003; Sprafkin et al., 2007; Sobanski et al., 2008b).

ADHD subtype differences on measures of executive function have also been investigated, albeit with inconclusive results. On the one hand, it has been argued that since inattention is common to both ADHD-I and ADHD-C subtypes, both should be impaired on tests of attention, processing speed, vigilance, and working memory (Chhabildas et al., 2001), and in line with this, studies have reported no differences in tasks of executive function between ADHD subtypes (Nigg et al., 2002; Geurts et al., 2005; Schweitzer et al., 2006). Nevertheless, it has been posited that ADHD-I subjects are fundamentally different from ADHD-C subjects in that inattention in ADHD-I stems from deficits in focused and selective attention, and differences in processing speed; whereas for ADHD-C subjects, deficits stem primarily from abnormal behavioral inhibition which affects sustained attention and affect regulation (Goodyear & Hynd, 1992; Barkley, 1997). In this regard, ADHD-C children have been reported to be more impulsive on tasks of response inhibition, while ADHD-I children have been reported to display slower retrieval and information processing, underarousal, and underactivity – albeit with inconclusive and mixed evidence (Barkley et al., 1990; 1992; Goodyear & Hynd, 1992; Lahey et al, 1998; Hartman et al., 2004; Calhoun & Mayes, 2005; Mayes et al., 2009; Querne & Berquin, 2009; Schmitz et al., 2010).

Despite clinical evidence on differences in the Inattentive and Combined subtypes of ADHD, the identification of genetic, neuroanatomical, and/or neurochemical factors that consistently differentiate between ADHD subtypes has been elusive (Baeyens et al., 2006), and, as such, the understanding of neurological mechanisms underlying the ADHD-I and ADHD-C phenotypes is poor. In 2012, Willcutt and colleagues published a meta-analysis of developmental course studies, functional impairment studies, co-morbidity studies, neuropsychological studies, neurophysiological studies, neuroimaging studies, family and twin studies, and molecular genetic studies to investigate the discriminant validity of DSM-IV ADHD subtypes (Willcutt et al., 2012). In this study, Willcutt and colleagues found that while ADHD subtype differences were evident with respect to concurrent mental disorders and some aspects of functional impairment; evidence for ADHD subtype differences in genetic, neuropsychological, neurophysiological, and neuroimaging studies were mixed (Willcutt et al., 2012). Based on
these findings, Willcutt and colleagues cast doubt on the validity of categorizing ADHD into ADHD-I and ADHD-C subtypes and, further, suggested that ADHD heterogeneity may be better understood as a function of DSM-IV inattention and hyperactivity-impulsivity symptom dimensions rather than as a function of ADHD nominal subtypes (Willcutt et al., 2012). It should be noted, however, that the identification of genetic, neuropsychological, neurophysiological, and neuroimaging factors that consistently differentiate between ADHD subtypes has been elusive due to the relative paucity of studies comparing ADHD subtypes – particularly in the adult population. Thus, as Willcutt and colleagues pointed out in one of their conclusions, “…the elimination of subtypes is premature, and the retention of the DSM-IV subtype structure would encourage additional research on this specific model of heterogeneity…” (Willcutt et al., 2012).

1.2.2.2 Changes introduced in the DSM-V and implications

Although the conceptualization of ADHD has not changed significantly since the publication of the DSM-IV in 1994, some updates to the diagnostic criteria of ADHD were introduced in the DSM-V to better accommodate for changes in the development of ADHD from childhood to adulthood, and to prevent underdiagnosis of ADHD due to excessively restrictive criteria (APA, 2013; Adam and Young-Walker, 2014). In this section, some of the more significant changes introduced in the DSM-V, and the implications of these changes to the findings presented in this dissertation are discussed.

i. The age of onset for ADHD was raised to 12, such that several symptoms of inattention and/or hyperactivity-impulsivity must have been present before the age of 12 (as opposed to 7 in the DSM-IV-TR, see section 1.2.2) for diagnosis of ADHD.

Implications: All the subjects recruited to the studies presented in this dissertation met this criterion (i.e. several symptoms of inattention and/or hyperactivity-impulsivity were present before the age of 12 for all subjects because the age of onset for ADHD was set to 7). However, the use of this DSM-V criterion would have led to the inclusion of subjects with later onset of ADHD (i.e. between the ages of 7 and 12) and, thus, the patient profiles of subjects recruited using this DSM-V criterion may have been
somewhat different from the patient profiles of subjects recruited to the studies presented herein.

ii. The threshold for diagnosis of ADHD in adults was lowered, such that five or more (as opposed to six or more in the DSM-IV-TR, see section 1.2.2) symptoms of inattention and/or hyperactivity-impulsivity must be present for diagnosis of ADHD.

Implications: All the subjects recruited to the studies presented in this dissertation met this criterion (i.e. all subjects had five or more symptoms of inattention and/or hyperactivity-impulsivity). However, the use of this DSM-V criterion would have led to the inclusion of subjects with less severe forms of ADHD (i.e. subjects with five symptoms of inattention and/or hyperactivity-impulsivity) and, thus, the symptom profiles of subjects recruited using this DSM-V criterion may have been somewhat different from the symptom profiles of subjects recruited to the studies presented herein.

iii. Specification for the severity of ADHD symptoms (i.e. mild, moderate, and severe) was added to the DSM-V.

Implications: This new criterion is not expected to affect the findings presented in this dissertation because correlation analyses (which, by default, take into consideration the severity of ADHD symptoms) were used to investigate relationships between ADHD symptoms and correlates of sleep such as circadian phase (see section 3.2.1.4) and polysomnography (see section 3.2.2.2) in ADHD subtypes.

iv. DSM-V emphasized the importance of obtaining ancillary information when diagnosing ADHD in adults.

Implications: The introduction of this new criterion is not expected to affect the results presented in this dissertation because ancillary information from a collateral was obtained for all subjects recruited to this study (see section 2.4.1).

v. The DSM-IV subtypes of ADHD (that is, Predominantly Inattentive Type, Predominantly Hyperactive-Impulsive Type, and Combined Type) are referred to as presentations (that is, Predominantly Inattentive Presentation, Predominantly Hyperactive-Impulsive Presentation, and Combined Presentation) in the DSM-V.
Implications: The change in denomination from ADHD *subtypes* in DSM-IV to ADHD *presentations* in DSM-V is meant to reflect the fact that current symptom presentation is likely to change over time due to the fact that inattention and hyperactivity-impulsivity symptoms follow different developmental trajectories, which in turn may lead to shifts in ADHD subtypes across development (Willcutt et al., 2012), as discussed in section 1.2.2. The mere change in denomination from *subtypes* to *presentations*, however, does not affect the stratification of subjects (be it into subtype groups or presentation groups) based on the presentation of inattention and/or hyperactivity-impulsivity symptoms and, thus, the introduction of this new criterion to DSM-V is not expected to affect the findings presented in this dissertation.

Overall, since the changes introduced in the DSM-V are only minor in relation to the DSM-IV-TR, ADHD subject profiles as defined by the DSM-IV-TR are not expected to differ significantly from patient profiles as defined by the DSM-V, and, thus, the findings presented in this dissertation are expected to be valid and relevant within the context of the DSM-V.

### 1.2.3 Neurobiology of ADHD

The advent of neuroimaging technologies such as Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI), Voxel-Based Morphometry (VBM), and Diffusion Tensor Imaging (DTI); as well as advances in the field of neuropharmacology have been pivotal in the understanding of neuroscience and, today, over two centuries after Chrichton’s publication “On Attention and its Diseases” (Crichton, 1798; Lange et al., 2010), the knowledge base of ADHD is considerably larger and more comprehensive. Nevertheless, the mechanisms underlying ADHD pathology are not fully understood and, in line with the highly heterogeneous nature of ADHD, several etiological factors that range from genetic polymorphisms to environmental insults – and everything in between – have been attributed to its pathology.
1.2.3.1 Brain structure

Neuroimaging studies conducted over the past couple of decades indicate that the ADHD brain is structurally different from healthy controls (see figure 1.1a). Meta-analytic studies and reviews of the cumulative evidence (Himelstein et al., 2000; Valera et al., 2007; Ellison-Wright et al., 2008; Cherkasova & Hechtman, 2009; Tripp & Wickens, 2009; Curatolo et al., 2010; Cortese, 2012) indicate that ADHD is associated with smaller brains, as well as volumetric reductions in the cerebellar vermis (Castellanos et al., 1996; 2001; Berquin et al., 1998; Mostofsky et al., 1998; Bussing et al., 2002; Hill et al., 2003) and structural abnormalities in the thalamus and the amygdala (Ivanov et al., 2010). Early speculation that some of the behavioral changes exhibited by post-encephalitic children were associated with physical changes in the basal ganglia (Bond & Partridge, 1926; Baumeister et al., 2012) were consistently confirmed by modern studies demonstrating that the caudate nucleus, putamen, and globus pallidus are significantly smaller in subjects with ADHD (Hynd et al., 1993; Castellanos et al., 1994; 1996; Aylward et al., 1996; Mataro et al., 1997; Valera et al., 2007; Ellison-Wright, 2008; Nakao et al., 2011).

Figure 1.1 The neurobiology of ADHD.
(a) ADHD has been reported to be associated with structural abnormalities in the thalamus and the amygdala; size reductions in the cerebellar vermis and basal ganglia; and reduced cortical volumes in the prefrontal, parietal, and temporal lobes. See text for more details. Figure adapted from Joseph, 2000.
(b) White matter also appears to be affected in ADHD, as studies indicate volumetric reductions of white matter in the corpus callosum and areas adjacent to the basal ganglia, as well as fiber tract abnormalities in frontal regions, cerebellum, corticospinal tract, superior longitudinal fasciculus, corona radiata, and internal capsule. See text for more details. Figure adapted from Midlands Technical College (No date).
The cortex, notably frontal areas, appears to play an important role in ADHD pathology also. Evidence stems from studies indicating decreased volumes in the prefrontal cortex (PFC) (Hynd et al., 1990; Castellanos et al., 1996; Casey et al., 1997, Filipek et al., 1997; Mostofsky et al., 2002) – particularly the inferior dorsolateral portions (Sowell et al., 2003), and in the lateral portions of the anterior and midtemporal cortices (Sowell et al., 2003). Cortical volume reductions have also been reported in regions of the parietal and temporal lobes (Castellanos et al., 2002; Carmona et al., 2005; Brieber et al., 2007; Wang et al., 2007).

Volumetric reductions in the cortex in ADHD are believed to be partly associated with deficits in cortical thickness. Studies have demonstrated that areas of the medial, superior and dorsolateral PFC, the precentral regions of the cortex (Sowell, 2003; Shaw et al., 2006; 2007), and the anterior and posterior association cortices (Narr et al., 2009) are thinner in children with ADHD than in healthy controls. Interestingly, there is considerable evidence to suggest that the developmental trajectory of cortical thickness is an important factor, not only in the pathology of ADHD in childhood, but also in clinical outcome as children grow into late adolescence.

Normal cortical development during childhood and adolescence is characterized by linear volumetric increases in white matter and occipital grey matter, as well and non-linear volumetric changes in grey matter, where the frontal, parietal, and temporal grey matter follow an inverted U-shaped developmental trajectory with volumetric increases in pre-adolescence and decreases in post-adolescence (Giedd et al., 1999). In a longitudinal study comparing children with ADHD according to clinical outcome (based upon persistence and severity of ADHD symptoms), children with better clinical outcome were found to have thicker left medial prefrontal and cingulate cortices at baseline (mean age 8 years) than those with worse outcome, as well as normalization in the right parietal cortical thickness at follow-up (mean age 14 years), suggesting that the remission of symptoms observed in some ADHD children as they enter adolescence may partly be attributed to normalization in the trajectory of cortical maturation (Shaw et al., 2006). Using peak cortical thickness as a measure of cortical maturation, the same group published a study a year later, demonstrating that while the sequential order of regional development is similar in children with ADHD and healthy controls, ADHD is characterized by a delay in cortical maturation – particularly in the lateral PFC – as the median age for reaching peak thickness in 50% of the observed cortical points was 7.5 years for healthy controls compared to 10.5 years for children with ADHD (Shaw et al., 2007).
While the findings of Shaw et al. (2007) imply that there is an eventual normalization of cortical thickness in ADHD with age, there is also evidence to suggest that at least in some subjects with ADHD, deficits in cortical thickness persists into adulthood, as Makris et al. (2007) found that adults with ADHD exhibit thinning in areas of the right inferior parietal lobule, dorsolateral prefrontal, and anterior cingulated cortices.

Studies suggest that reduced cortical volume in ADHD is also associated with reduced surface area and folding in the cortex. Li et al. (2007) found that cortical complexity and folding in the left hemisphere were reduced in children with ADHD, and more recently, using gyrification index (GI) – the ratio of inner and outer contour of the cortex – in MRI studies, Wolosin et al. (2009) found that while cortical thickness was comparable between children with ADHD and healthy controls; cortical volume, surface area, and folding were significantly reduced in children with ADHD.

Lately, white matter has also been the focus of research in the field of ADHD neuroanatomy (see figure 1.1b). As reviewed by Himelstein (2000), Curatolo (2009), Shaw & Rabin (2009), Tripp & Wickens (2009), and Cortese (2012), studies indicate that ADHD is associated with whiter matter volumetric reductions in the corpus callosum (Hynd et al., 1991; Giedd et al., 1994; Semrud-Clikeman et al., 1994; Baumgardner et al., 1996; Lyoo et al., 1996) and regions adjacent to the basal ganglia (Overmeyer et al., 2001; McAlohan et al., 2007). As well, studies on the integrity of white matter fibers indicate tract abnormalities in frontal regions of the brain and in the cerebellum (Ashtari et al., 2005; Davenport et al., 2010; Kobel et al., 2010), in the corticospinal tract and in the superior longitudinal fasciculus (Hamilton et al., 2008), in the anterior corona radiata as well as in the anterior limb and superior region of the internal capsule (Pavuluri et al., 2009), in the isthmus of the corpus callosum (Cao et al., 2010), and in white matter tracts that connect prefrontal and parieto-occipital areas with the striatum and cerebellum (Silk et al., 2009).

### 1.2.3.2 Brain function

In addition to structural abnormalities, the ADHD brain is associated with functional abnormalities. Studies on the ADHD brain during resting state indicate frontal and striatal
hypoperfusion; while studies of brain function during cognitive tasks designed to assess working memory, interference control, decision-making, reward processing, and attention indicate reduced activation in the striatum and frontal regions of the brain such as the dorsal anterior cingulate, dorsolateral prefrontal, inferior prefrontal, and orbitofrontal cortices (as reviewed by Dickstein et al., 2006; Chersakova et al., 2009; Cortese, 2012). ADHD symptomatology is also believed to be associated with functional abnormalities in areas of the brain that subserve executive functions regulated by frontostriatal networks. This is evidenced by studies indicating reduced cerebellar activity, as well as deficits in parietal areas such as the precuneus, posterior cingulate gyrus, parietal association cortex, left inferior parietal lobule, and posterior portion of the left superior temporal gyrus during cognitive tasks testing various aspects of inhibition and attention; and by studies indicating deficits in areas of the temporal lobe such as the middle temporal gyrus, hippocampal gyrus, and left insula during cognitive tasks assessing attention processing of verbal auditory stimuli and decision making in short-term versus long-term rewards (as reviewed by Dickstein et al., 2006; Cherkasova et al., 2009; Cortese, 2012). Altogether, the findings discussed in this section point to ADHD as a condition associated with functional abnormalities in networks regulated by frontostriatal areas.

1.2.3.3 Signaling

Adequate brain function is dependent, not only on intact brain structures but also on proper intra- and inter-neuronal communication mediated in part by neurotransmitter systems. For the ADHD brain, abundant research indicates that signaling of the catecholamines dopamine (DA) and norepinephrine (NE) is compromised.

A principal role for catecholamines in the pathology of ADHD was first proposed in 1970 by Conan Kornetzky, who theorized that ADHD medications act by inhibiting NE synthesis, turnover, or release and, thus, concluded that catecholamine regulation must be affected in ADHD (Kornetzky, 1970; Baumeister et al., 2012). Exactly how catecholamine regulation is affected, however, is not well understood, as catecholamine signaling systems are quite complex and the actions of DA and NE depend, not only on which receptors these catecholamines bind to, but also on the location of these receptors.
1.2.3.3.1 Regulation of DA and NE signaling

DA exerts its actions through activation of DA receptor subtypes D₁ to D₅, which are classified into the D₁-like receptor family (D₁ and D₃) and the D₂-like receptor family (D₂, D₃, and D₄) (Arnsten, 2006). The D₁-like receptor family couples to the G protein Gₛ, which leads to an increase in the concentration of the second messenger cyclic adenosine monophosphate (cAMP) in the cell via activation of adenylyl cyclase; while the D₂-like receptor family couples to Gᵢ, which inhibits adenylyl cyclase (Arnsten, 2006). Of note, the D₂ receptor can be found postsynaptically, where it acts as a classic receptor, or presynaptically, where it plays the role of an autoreceptor, homeostatically regulating the amount of DA that is released into the synapse. Also, D₄ receptors are found in γ-aminobutyric acid (GABA)-ergic interneurons, where they inhibit GABA release (Arnsten, 2006).

NE exerts its actions through activation of NE receptors α₁ and α₂, and β₁ to β₃; and the DA receptor D₄ (Tripp & Wickens, 2009). Of note, the actions of NE receptors α₁, α₂, and β₁ differ in different regions of the brain: in the PFC, activation of α₂ receptors improves, while activation of α₁ impairs PFC functions (Arnsten, 2000). In posterior and subcortical regions, activation of α₁ and β₁ receptors improves while activation of α₂ impairs functions regulated by these regions, which include the processing of visual features, directing focus to novel stimuli, and long term memory consolidation (Arnsten, 2000).

Both dopaminergic and noradrenergic receptors produce an inverted U-shaped dose response curve (Berridge & Waterhouse, 2003; Arnsten et al., 2006). Optimal dopaminergic signaling is reported to improve working memory by inhibiting the processing of irrelevant information, while optimal noradrenergic signaling improves working memory by increasing signals in the PFC (Arnsten et al., 1994; 2006; Berridge & Waterhouse, 2003). Noradrenergic and dopaminergic neurons are thought to interact to carefully regulate extra-neuronal concentrations of DA and NE (Yamamoto & Novotney, 1998; Biederman & Spencer, 1999; Devoto et al., 2001; 2003; 2004; Carboni et al, 2006). Thus, catecholaminergic signaling pathways work together to increase the signal to noise ratio.

Activation of dopaminergic and noradrenergic receptor subtypes is partly regulated by DA and NE transporters (DAT and NET, respectively), which modulate the concentration of...
catecholamines at the synapse (Madras et al., 2005). DAT and NET are transmembrane re-
uptake proteins that sequester neurotransmitters back into the neuron, thereby clearing 
exttracellular DA and NE, and limiting their actions at the synapse (Madras et al., 2005). While 
DAT sequesters DA back into dopaminergic neurons, NET sequesters both NE and DA back 
into noradrenergic neurons (Madras et al., 2005).

1.2.3.3.2 Pharmacodynamics of ADHD medications

It is now known that the first-line ADHD medications – *i.e.* methylphenidate (MPH), 
dextroamphetamine (DEX), and atomoxetine (ATX) – target DAT and NET to increase the 
concentrations of extracellular DA and NE. The mechanisms underlying these effects, however, 
differ somewhat between the three drugs.

Both MPH and ATX are reuptake inhibitors, but whereas MPH blocks both DAT and NET, 
ATX selectively blocks NET (Wilens, 2006). In the frontal cortex, where NET density is higher 
than DAT density, MPH and ATX have similar effects because they both target NET and, in 
turn, NET has a high affinity for both DA and NE, meaning that administration of either MPH 
or ATX will lead to an increase in extracellular NE and DA (Eshleman et al., 1999; Bymaster et 
al., 2002; Madras et al., 2005). Conversely, ATX has no effect in the striatum, where DAT 
density is high while NET density is very low (Gehlert et al., 1995; Madras et al., 2005).

The mechanism of action underlying the therapeutic effects of DEX is a little more complex. 
DEX is a substrate analog that competes with NE and DA for transport into the presynaptic 
terminal. As DEX is transported into the neuron in place of NE and DA, the actions of these 
catecholamines in the synapse are prolonged (Heal et al., 2009) and intracellular Ca\(^{2+}\) increases, 
leading to catecholamine efflux, which further potentiates the actions of catecholamines (Gnegy 
et al., 2004; Madras et al., 2005). Moreover, once inside the cell, DEX increases cytoplasmic 
catecholamine by inhibiting monoamine oxidase and by being transported into catecholamine 
storage vesicles, which promotes the release of catecholamines into the cytoplasm (Green & el 
Hait, 1978; Sulzer & Rayport, 1990; Madras et al., 2005; Heal et al., 2009). In turn, the surge in 
cytoplasmic catecholamine activates the reverse transport of DA and NE via the DATs and
NETs, thereby further increasing extracellular catecholamine concentrations (Raiteri et al., 1979; Madras et al., 2005; Heal et al., 2009).

The clinical implications of region-specific differences in the pharmacology of ATX, DEX, and MPH are currently not well understood. ATX is stipulated to be a better choice for patients with co-morbid drug abuse disorders because it has no drug abuse potential due to its low potency at DAT in the basal ganglia (Heil et al., 2002; Madras et al., 2005; Hazell et al., 2011). ATX is also stipulated to be a better choice for patients with co-morbid anxiety, depression, and Tourette syndrome due to its selectivity for NET (Geller et al., 2007; Spencer et al., 2008; Hazell et al., 2011). With regards to treating the core symptoms of ADHD, however, meta-analytic studies indicate that ATX, MPH, and DEX have comparable therapeutic efficacies (Kratochvil et al., 2002; Wang et al., 2007; Garnock-Jones & Keating, 2009; Hanwella et al., 2011). Given that ATX, DEX, and MPH have similar effects in the frontal cortex but not in the striatum, the comparable efficacies of these drugs suggest that correcting catecholamine tone in the frontal cortex may be more important in the treatment of ADHD-symptoms than correcting catecholamine tone in the striatum (Madras et al., 2005).

1.2.3.3.3 ADHD: excess or deficit of catecholamines?

There has been much debate and controversy over the issue of catecholamine regulation in ADHD: some researchers believe that ADHD is a disorder of deficient catecholamine signaling while others believe that ADHD is associated with excessive signaling. Indeed, both too much and too little catecholamine signaling can have detrimental effects on PFC functions (Figure 1.2). In the case of DA, too little DA will result in inadequate suppression of irrelevant signals, while too much DA will result in excessive inhibition of network connections and suppression of neuronal firing (Vijayraghavan et al., 2007; Arnsten, 2009). In the case of NE, too little NE will result in insufficient activation of α2 adrenergic receptors leading to low responsiveness of PFC neurons to stimuli of interest, while too much NE will lead to the activation of the lower affinity α1 and β1 receptors, suppressing PFC functions and activating the more automatic and habitual responses of posterior and subcortical structures (Arnsten, 2000).
Evidence in favor of a theory of catecholamine deficiency in ADHD comes from a number of studies from different fields. Animal studies of DA lesioned rats and DAT knockout mice have shown that these mutations result in an ADHD-like phenotype (Van der Kooij & Glennon, 2007). In humans, ADHD is associated with volumetric reductions in the DA receptor-rich caudate nucleus and globus pallidus, as well as reduced activation of the cortico-striatal-thalamic DA pathway (Swanson et al., 2007). Moreover, PET studies indicate that reduced availability of D$_2$/$D_3$ receptor subtypes and increased DAT binding in the right caudate is associated with inattention (Prince, 2008) and frontal hypoactivation is corrected by ADHD medications – suggesting deficiencies in catecholamine signal transduction in ADHD (Lee et al., 2005a).

Given that the primary effect of ADHD medications is to increase the concentration of catecholamines in the synapse, it would be reasonable to deduce that ADHD is caused by a
deficiency of catecholamine signaling. Indeed, PET studies utilizing radiolabelled MPH and raclopride (a D₂ antagonist) led by Volkow et al. (1998; 2002) demonstrated that MPH binds to DAT, leading to an increase in extrasynaptic DA and occupancy of D₂ receptors in the striatum, and this was interpreted to mean that MPH exerts its therapeutic effects by increasing DA and, thus, correcting an underlying DA deficit (Swanson et al., 2007). Such an interpretation, however, may be an oversimplification in view of the fact that factors such as the effects of pre-versus postsynaptic receptors and tonic versus phasic secretion of neurotransmitters must be taken into account when considering the end result. As such, both Solanto (1998; 2002) and Seeman & Madras (1998) proposed a DA excess theory of ADHD.

According to the DA excess theory of ADHD, there are low basal levels of extracellular DA due to low tonic secretion of DA and subsequent phasic overshoot of DA which leads to hyperactivity, poor impulse control, and excessive novelty seeking behaviour in ADHD. In explaining the therapeutic effects of stimulant medications, it has been proposed that administration of stimulants leads to an increase in the basal levels of extracellular DA by blockage of DAT, and that this increase leads to the activation of presynaptic D₂ receptors, which in turn modulates DA secretion to lower phasic bursts, effectively reducing hyperactive/impulsive behaviours.

An important consideration is that D₂ autoreceptors are found in neurons that emanate from the substantia nigra, but not in neurons that emanate from the ventral tegmental area (VTA) (Meador-Woodruff et al., 1994), suggesting that modulation of DA in the nigrostriatal pathway differs from modulation of DA in the mesolimbic and mesocortical pathways. The mesocortical pathway, which extends dopaminergic neurons from the VTA to the frontal cortex, is involved in the regulation of cognitive functions; while the nigrostriatal pathway, which extends dopaminergic neurons from the substantia nigra (par compacta) to the striatum is involved in the regulation of motor behaviour. Based on these considerations, Castellanos (1997) proposed that ADHD is associated with two distinct abnormalities of DA modulation:

- Underactivity in the frontal cortex due to low tonic/low phasic DA secretion leading to inattention, where administration of stimulants would lead to an increase in the activation of post-synaptic receptors in the PFC; and
• Overactivity in the striatum due to low tonic/high phasic DA secretion leading to hyperactivity/impulsivity, where administration of stimulants would lead to an increase in basal synaptic DA, activation of presynaptic D₂ receptors, and subsequent attenuation of phasic DA burst.

It is clear from the studies discussed in this section that signaling in ADHD is complex. More recent studies have reported that, in addition to catecholamine signaling, cholinergic (Kollins et al., 2005; Potter et al., 2006; Huizink et al., 2009) and serotonergic (Muller et al., 2008) signaling pathways are also affected in ADHD. This suggests an intricate interplay of signaling pathways in the neuropathology of ADHD.

1.2.4 Etiological factors

1.2.4.1 Genes

The cumulative evidence from family, twin, and adoption studies has established ADHD as a highly heritable condition for which genetic factors are speculated to explain 60-80% of the variance and, thus, ADHD has been the target of several molecular genetics studies over the past 15 to 20 years (Faraone et al., 2005; Wood et al., 2010). The search for gene polymorphisms, however, has not been without difficulties, and while candidate gene association studies have identified a number of significant gene variants in ADHD, results have not always been replicated, or statistical significance has been lost in meta-analyses. Moreover, for gene variants well-established to be associated with ADHD, the individual genetic contributions to ADHD variance have been found to be very low, suggesting that ADHD phenotype is the result of complex polygenic transmission patterns (Curatolo et al., 2009; Gizer et al., 2009; Tripp & Wickens, 2009; Faraone & Mick, 2010).

Candidate genes in association studies are chosen based on their potential implications in the pathology of ADHD and, thus, genes directly or indirectly involved in catecholaminergic signaling have been common targets. Studies examining potential associations between ADHD pathology and genes encoding for the receptors, transporters, and enzymes of DA, NE, serotonin (5-HT), acetylcholine (Ach), and glutamate (Glu) have yielded variable results, with meta-analyses indicating strong associations between ADHD and polymorphisms in the dopamine D₄
and D₃ receptors genes (*DRD4* and *DRD5*, respectively), the dopamine transporter gene (*DAT1*), the serotonin receptor (*HTR1B*) and transporter (*5-HTT*) genes, the neuronal acetylcholine receptor subunit α₄ gene (*CHRNA4*), and the synaptosomal associated protein of 25kD gene (*SNAP25*) (Gizer et al., 2009; Faraone and Mick, 2010). Table 1.2 shows the relevance of these genes to ADHD, as well as the types, locations, and postulated effects of the polymorphic variants or “risk alleles” that occur at higher frequencies in ADHD.

The exact relationships between the gene variants listed in Table 1.2 and ADHD pathology is not well understood, partly because ADHD is a polygenic and heterogeneous condition, where multiple combinations of individual genetic variants with small effect sizes may give rise to the same phenotype, but also because some of the polymorphisms are located in areas that end up being spliced out (intron 8 VNTR in *DAT1*, intron 2 SNP in *CHRNA4*) or untranslated (SNP in 3’ untranslated region (UTR) in *SNAP25*, VNTR in 3’ UTR in *DAT1*), making it difficult to understand whether or how these polymorphisms affect the final gene product. As a result, while one may speculate about the relevance of these gene variants, the nature of their contribution to ADHD pathology is currently not well understood.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Relevance to ADHD</th>
<th>Polymorphism</th>
<th>Risk Allele</th>
<th>Postulated Effects</th>
</tr>
</thead>
</table>
| **DRD4** | Highly expressed in frontal lobe regions speculated to be affected in ADHD          | VNTR in exon 3            | 7R          | • Smaller prefrontal grey matter (Durston et al., 2004)  
• Cortical thinning in the right posterior parietal lobe and better clinical outcome (Shaw et al., 2007)  
• Weakened sensitivity to endogenous DA, presumably leading to excessive GABA release and suppression of pyramidal cell firing (Sunohara et al., 2000; Tahir et al., 2000; Swanson et al., 2007)  
• Allele may affect cognitive performance (poor performance reported by Kieling et al., 2006; Langley et al., 2004; no effect reported by Bellgrove et al., 2005; Manor et al., 2002; Swanson et al., 2000)  
• Gene may be associated with inattention (Association reported by Rowe et al., 2001 and Levitan et al. 2004; no association reported by Todd et al., 2005 and Mill et al., 2005)  
• Gene may be associated with novelty seeking (Association reported by Benjamin et al., 1996 and Ebstein et al., 1996; no association reported by Lynn et al., 2005) |
<p>|      | SNP in the promoter                                                                | T                         |             | • Reduced promoter activity in transfected cells, thus may affect expression in ADHD (Okuyama et al., 1999)                                                                 |
| <strong>DRD5</strong> | Involved in induction of long-term potentiation related to novel events             | Dinucleotide repeat in 5’ flanking region | 148 base pairs | • Lower hyperactivity scores (Mill et al., 2005)                                                                                                    |
| <strong>SNAP-25</strong> | Regulation of neurotransmitter release, axonal growth and synaptic plasticity     | SNP in 3’ UTR              | T           | • In mice, gene mutation leads to spontaneous hyperactivity and deficits in DA release in dorsal striatum (Wilson, 2000)     |</p>
<table>
<thead>
<tr>
<th>Gene</th>
<th>Relevance to ADHD</th>
<th>Polymorphism</th>
<th>Risk Allele</th>
<th>Postulated Effects</th>
</tr>
</thead>
</table>
| S-HTT | Expressed in areas implicated in attention, memory and motor activity such as amygdala, hippocampus, thalamus, putamen and anterior cingulate cortex | VNTR in promoter | Long | • More rapid serotonin uptake, thus lower extracellular serotonin and action
• Involved in impulsivity/hyperactivity (Halperin et al., 1997; Spivak et al., 1999; Stein et al., 1993; Gainetdinov et al., 1999) |
| HTR1B | Highly expressed in dRN (sleep/wake), striatum and dorsolateral PFC (Ichikawa et al., 2005) | SNP in exon 1 | G | • Unknown |
| DAT1 | Regulation of extracellular DA levels | VNTR in intron 8 | 6R | • Unknown |
|      |                | VNTR in 3’ UTR | 10R | • 10R/10R haplotype associated with smaller caudate nucleus (Durston et al., 2004)
• May be more strongly associated with hyperactivity/impulsivity than with inattention (Waldman et al., 1998; Swanson et al., 2000; Mill et al., 2005) |
| CHRNA4 | Nicotine alters dopamine activity. Administration improves attention, working memory and reduces symptom severity (Levin 2002; Wilens et al., 2006; Grady et al., 1992 from Gizer) | SNP in exon 2 | T | • Unknown |
|      |                | SNP in intron 2 | T | |

**Abbreviations:** 6R – 6 repeats; 7R – 7 repeats; 10R – 10 repeats; DA – dopamine; DRD4 – dopamine receptor D4 receptor gene; G – Guanine; GABA – gamma-aminobutyric acid; SNP – single nucleotide polymorphism; T – thymine; UTR – untranslated region; VNTR – variable number of tandem repeats

### 1.2.4.2 Environmental factors

In line with the heterogeneous nature of ADHD, a number of environmental factors have also been reported to contribute to ADHD pathology. As thoroughly reviewed by Swanson et al.
(2007), Curatolo et al. (2008), and Millichap (2008), well-replicated factors found to be associated with ADHD or ADHD-symptomatology are:

- Prenatal exposure to lead (Minder et al., 1994; Tuthill, 1996), cigarette compounds (Millberger et al., 1996; Thapar et al., 2003), and alcohol (Aronson et al., 1997; Knopik et al., 2006; D’Onofrio et al., 2007)
- Low birth weight and/or premature birth (Bhutta et al., 2002; Lahti et al., 2006)
- Pre-, peri-, and/or post-natal viral infections, including, but not limited to, human immunodeficiency virus (Nozyce et al., 2006), entevirus 71, measles, varicella, rubella (Arpino et al., 2005; Dale et al., 2003), and herpes virus 6 (Millichap & Millichap, 2006; Pineda et al., 2007).
- History of thyroid function abnormalities (Hauser et al., 1993; Stein & Weiss, 2003)

Additionally, there is variable/inconclusive evidence on associations between ADHD pathology and dietary deficiencies in nutrients that include, but are not limited to, iron (Millichap et al., 2006), zinc (Akhondzadeh et al., 2004; Arnold & DiSilvestro, 2005), omega-3 fatty acids (Richardson & Montgomery, 2005), and iodine (Vermiglio et al., 2004).

1.2.4.3 Gene-environment interactions

Following ground-breaking research on the moderating effects of environmental factors on the contributions of serotonin transporter and monoamine oxidase A gene polymorphisms to the pathology of depression (Risch et al., 2009; Kim-Cohen et al., 2006), interest concerning the effects of gene-environment interactions spread over to the study of ADHD pathology. Although there are currently only a few published studies reporting significant interactions in ADHD, as reviewed by Swanson et al. (2007) and Nigg et al. (2010), there is evidence to suggest that prenatal exposure to nicotine is associated with more damage in subjects homozygous for the 10R allele of the DAT1 (Kahn et al., 2003); that the deleterious effects of both 6R and 10R alleles of DAT1 are compounded when carriers are subject to social adversity in the forms of low income, in-home conflicts, or large family (Laucht et al., 2007; Stevens et al., 2009); and that the deleterious effects of the long repeat allele of 5-HTT are compounded.
when carriers are subject to social adversity and/or marital conflict (Retz et al., 2008; Nikolas et al., 2010).

### 1.2.5 Co-morbidities of ADHD

In children, ADHD is frequently associated with a number of symptoms common to other disorders or symptom categories such as aggression, ODD, and CD (Cantwell, 1985); substance abuse and personality disorders (Gittelman et al., 1985); tic disorders (Plessen et al., 2007); Asperger’s syndrome (Nyden et al., 2001; Gillberg et al., 2002; Holtmann et al., 2005; Brieber et al., 2007); Tourette’s syndrome (Schuerholz et al., 1997; Spencer et al., 2001; Cortese et al., 2008); BD (Wozniak et al., 1995; Faraone et al., 1997; Sachs et al., 2000); speech and language disorders (Giddan 1991; McGrath et al., 2008); and learning disabilities (LD) (Gomez & Condon 1999; Doyle et al., 2001; Seidman et al., 2001; Brook & Boaz, 2005; Jakobson & Kikas, 2007; McNamara et al., 2008).

In adults, ADHD-associated symptoms such as procrastination, poor time management skills, anger problems, and impatience; along with maladaptive lifestyles are thought to increase the risk of developing co-morbidities such as major depressive disorders, anxiety disorder, and substance abuse (Shekim et al., 1990; Milberger et al., 1995; Biederman et al., 1995; 1999; Secnik et al., 2005; Turgay et al., 2008).

Sleep disorders are also common co-morbidities of both childhood and adult ADHD. Estimated to occur in 25-50% of children and over half of adults with ADHD (Dobson & Zhang, 1999; Gruber et al., 2000; Hvolby et al., 2008), initial interest in the topic developed from the finding that sleep deprivation was associated with hallmarks of ADHD, including deficits in cognitive performance, hyperactivity, irritability, and inattention (Guilleminault et al., 1982; Weissbluth et al., 1983; Zuckerman et al., 1987; Kotagal et al., 1990; Ali et al., 1993; 1996; Minde et al., 1994; Chervin et al., 1997; 2001; 2002a; 2002b; 2003; Gozal & Pope, 2001; O’Brien et al., 2003a; Van Donger et al., 2003) – suggesting a functional relationship between sleep and ADHD pathology.
1.3 Sleep

1.3.1 A selective historical account of sleep medicine

Sleep is perhaps one of the most fascinating aspects of the human condition, that has evoked a scientific and philosophic curiosity that quite possibly dates back to the beginning of man as a rational being. Man’s fascination with sleep can be seen throughout history, from Greek mythology stories about Morpheus, Phobetor, and Phantasos, who were servants of Hypnos (the god of sleep) that manifested in the mortal realm in the form of dreams; to passages in the Hebrew Bible and the Qur’an describing the story of Joseph, who experienced prophecies from God in the form of dreams; to references in the works of Shakespeare, of which perhaps one of the most famous and beloved is in Hamlet’s soliloquy:

“…To die, to sleep--
No more--and by a sleep to say we end
The Heartache, and the thousand natural shocks
That flesh is heir to. ’Tis a consummation
Devoutly to be wished...”.

The scientific inquiry as to the nature and mechanisms of sleep also dates back to ancient times. Texts on early theories on the mechanisms of sleep can be found as early as 500BCE, when Alcmaeon of Croton proposed that “…sleep is produced by the withdrawal of blood away from the surface of the body…”, and around 350 BCE, when Aristotle wrote *On Sleep and Sleeplessness* – a composition in which he conjectured on the nature, function, and mechanisms of sleep and dreams (excerpt obtained from Kirsch, 2011). By 300 BCE, it is apparent from the works of Hippocrates that the circadian nature of sleep (“…with regard to sleep (…) the patient should wake during the day and sleep during the night. If this rule be anywise altered it is so far worse…”) and the importance of sleep to mental health (“…insomnolency is connected with sorrow and pains, or that he is about to become delirious…”) were already suspected (excerpts obtained from Kirsch, 2011).
The Scientific Revolution of the 17th century also marked an important period in the study of sleep. During this time, René Descartes proposed a model of sleep in which the pineal gland served as a gatekeeper of sleep and wakefulness through the differential production of “animal spirits” throughout the nycthemeron (Kirsch, 2011) – a proposal that is especially remarkable, considering that the pineal gland indeed produces differential amounts of melatonin during the day and night as part of the system that regulates sleep-wake cycles as discussed in section 1.3.3.3. It was also during the Scientific Revolution that the innovative works of Thomas Willis were published, with new theories on sleep disorders such as sleep-walking, insomnia, narcolepsy, and restless legs (Kirsch, 2011).

The real bulk of scientific discovery in the field of sleep medicine, however, came during the 20th century; with Constantin von Economo’s identification of brain areas involved in the regulation of sleep and wakefulness in the 1920’s; Hans Berger’s use of an “Elektrenkephalogramm” to measure electrical activity of the human brain in 1925; Loomis and colleagues’ identification of non-rapid eye movement (NREM) sleep in 1937; and Dement and Kleitman’s discovery of a previously unidentified stage of sleep called rapid eye movement (REM) sleep in 1953 – all of which cleared the path for a more in-depth study of the mechanisms underlying sleep and its disorders (Kirsch, 2011; Bailey & Attanasio, 2012).

1.3.2 Current definition of sleep

Behaviorally, sleep is a state of being that – contrary to wakefulness, which is associated with logical and progressive thought processes, continuous and voluntary movements, vivid sensations, and externally generated perception – is characterized by a reduction in voluntary motor activity, decreased response to stimulation, stereotypic posture, and significantly distinct thought processes (Pace-Schott & Hobson, 2002; Fuller et al., 2006; Datta, 2010).

From a strictly physiological perspective, sleep and wakefulness are characterized by differences in the bio-electrical activities of excitable cells found in the cerebral cortex, the eyes, and the muscles, which can be measured by the electrophysiological techniques of EEG, electro-oculography (EOG), and electromyography (EMG), respectively (Pace-Schott & Hobson, 2002; Patil, 2010).
Table 1.3 EEG characteristics of sleep and wakefulness

<table>
<thead>
<tr>
<th>STAGE</th>
<th>EEG FREQUENCY</th>
<th>EEG MARKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAKEFULNESS</td>
<td>Full 14-30 Hz (beta waves)</td>
<td>Desynchrony</td>
</tr>
<tr>
<td></td>
<td>Quiet rest 8-12 Hz (alpha waves)</td>
<td>Desynchrony</td>
</tr>
<tr>
<td>NREM</td>
<td>Stage 1 4-7 Hz (theta waves)</td>
<td>Sleep spindles, K-complexes</td>
</tr>
<tr>
<td></td>
<td>Stage 2 1-3 Hz (delta waves)</td>
<td>Synchrony</td>
</tr>
<tr>
<td>REM</td>
<td>mixed</td>
<td>Desynchrony</td>
</tr>
</tbody>
</table>

By EEG measures, sleep can be divided into two stages: REM sleep, which is associated with vivid dreaming and high-frequency/low-voltage cortical activity; and NREM sleep, which is associated with low-frequency/high-voltage cortical activity (McCarley, 2007). In turn NREM sleep can be divided into three stages: stage 1 sleep, stage 2 sleep, and slow wave sleep (SWS). Each of these stages of sleep is associated with its own set of EEG markers (Table 1.3) and during the night, NREM sleep and REM sleep alternate following an ultradian cycle. Each cycle lasts 90-100 minutes, and while SWS invariable precedes REM sleep in healthy subjects, SWS predominates during the first half of the night, constituting up to 80% of sleep time during the first half of the night; and REM sleep, which alternates with stage 2 sleep, predominates during the second half of the night (Peigneux et al., 2001).

1.3.3 Regulation of sleep-wake cycles

One of the pioneers of sleep research was Constantin von Economo, whose studies were instrumental in the identification of brain areas involved not only in the pathology of ADHD, but also in the regulation of sleep-wake cycles. In a series of articles published between 1925 and 1931, von Economo noted that subjects suffering from encephalitis lethargica could be divided into subjects who slept excessively – some as much as 20 hours a day – and subjects who only slept a few hours a day; and with his studies of post-mortem brains, von Economo deduced for the first time the roles of the brainstem and the hypothalamus in the regulation of sleep and wakefulness (Saper et al., 2005; Triarhou, 2006).
It is now known that the regulation of sleep-wake cycles is governed by a number of brain nuclei that regulate not only the transitions from sleep to wake and vice-versa, but also the timing of these transitions, as discussed in sections that follow.

### 1.3.3.1 The flip-flop switch mechanism

Wakefulness (along with alertness and attention) is a dynamic state that is achieved by the activation of excitatory neurons in six important loci of the brain: the laterodorsal tegmental (LDT) and pedunculopontine (PPT) nuclei, the dorsal (dRN) and medial (mRN) raphe nuclei, the tuberomammillary nucleus (TMN), ventral periaqueductal grey matter (vPAG), and the locus coeruleus (LC). The neural pathways and mechanisms that exist between these loci are collectively referred to as the ascending reticular activating system (ARAS), and this system is organized into two major branches: a branch of cholinergic neurons that extends from the PPT/LDT to thalamocortical nuclei and the reticular nucleus; and a branch of monoaminergic neurons which extend from the dRN/mRN, TMN, vPAG, and LC to the thalamus, lateral hypothalamus (LH), basal forebrain (BF), and cerebral cortex (Pace Scott & Hobson, 2002; Aloe et al., 2005; Saper et al., 2005) (Figure 1.3a). Activation of these branches leads to the release of wake promoting factors that act together to achieve a dynamic state of consciousness appropriate for the environmental demands.

The wake promoting actions of the ARAS are opposed by the ventrolateral preoptic nucleus (VLPO), an area of the brain involved in the promotion of sleep, that contains GABAergic neurons that project to and, thus, inhibit the TMN, LC, and raphe nuclei (RN) (Fuller et al., 2006) (Figure 1.3b). In turn, the TMN, LC, and RN project GABAergic, noradrenergic, and serotonergic neurons that have inhibitory effects on the VLPO (Gallopin et al., 2000; Chou et al., 2002). The result of these interactions is a mutually inhibitory mechanism between ARAS and VLPO that bears a resemblance to the movements of a seesaw – when the activation of the ARAS is higher than the activation of the VLPO, wakefulness occurs and, alternatively, when activation of the VLPO becomes higher than that of the ARAS, a switch to the sleep state takes place. This mechanism, referred to as the “flip-flop” switch mechanism, is responsible for the transition from sleep to wakefulness and vice-versa (Figure 1.4) (Saper et al, 2005).
Figure 1.3 Regulation of sleep by the ascending reticular activating system and the ventrolateral preoptic nucleus.
(a) The ascending reticular activating system (ARAS) consists of cholinergic (red) and monoaminergic (green) neurons that extend to different regions of the brain. (b) The ventrolateral preoptic nucleus (VLPO) (blue) projects inhibitory GABAergic neurons to nuclei of the ARAS. Figures adapted from Saper et al., 2005.
Abbreviations: LC – locus coeruleus; LDT – laterodorsal tegmental nucleus; PPT – pedunculopontine nucleus; RN – raphe nuclei; VLPO – ventrolateral preoptic nucleus; vPAG – ventral periaqueductal grey; TMN – tuberomammillary nucleus

Figure 1.4 The flip-flop switch mechanism.
(a) Sleep occurs when activation of the ventrolateral preoptic nucleus (VLPO) is higher than activation of the ascending reticular activating system (ARAS). (b) Wakefulness occurs when activation of the ARAS is higher than activation of the VLPO. Figure adapted from Saper et al., 2005.
An additional component that is important in the flip-flop mechanism is orexin (ORX). Also known as hypocretin, ORX is a neuropeptide synthesized in the LH and ventromedial hypothalamic nucleus (VMH), with roles in the maintenance of alertness and motor activity (Lee et al., 2005b; Mileykovskiy et al., 2005). ORX has an excitatory effect on the ARAS and, as such, activation of ORX neurons consolidates wakefulness and prevents unwanted transitions to sleep (Peyron et al., 1998; Saper et al., 2005). In line with this, animal studies have shown that faulty ORX signaling results in symptoms of narcolepsy, characterized by attacks of cataplexy and hypersomnia during the biological day (Chemelli et al., 1999; Peyron et al., 2000; Thannickal et al., 2000).

While the flip-flop switch mechanism regulates the transition from sleep to wake and vice-versa, there are upstream mechanisms that regulate the timing as well as the direction of the switch. According to the two step process model of sleep regulation – a widely accepted paradigm developed by Alexander Borbely in 1982 – there are two processes that affect cycling through sleep and wakefulness: a homeostatic process – process S – which can be described as a homeostatic “drive” or need for sleep; and an endogenous circadian process – process C – which coordinates sleep and wakefulness to the time of day (Borbely, 1982; Borbely & Achermann, 1999; Peigneux et al., 2001).

The homeostatic drive to sleep increases exponentially with time awake, and the initiation and maintenance of sleep leads to exponential decrements in process S (Fuller et al., 2006). On the other hand, process C is characterized by fluctuations in wakefulness, such that levels increase gradually throughout the daytime – albeit with a dip experienced in the mid afternoon –, reaching maximal levels in the early evening that gradually decrease to a nadir at around 4-6AM (Borbely, 1982; Cajochen et al., 2010).

According to the opposing model – a paradigm complementary to Borbely’s, proposed in 1993 (Edgar et al., 1993) – cycling through sleep and wakefulness is a result of the interaction of process S and process C: wakefulness is maintained in spite of an increasing drive to sleep due to the increase in alertness associated with the C process, and during the biological night, sleep is maintained in spite of the decreasing need for sleep due to the attenuation of wakefulness associated with the C process (Figure 1.5).
Figure 1.5 The oppositional model of sleep regulation. The homeostatic drive to sleep, or process S, increases with time awake and dissipates with sleep. During the day, the sleep homeostat is counteracted by a diurnal increase in wakefulness under process C. Wakefulness levels decrease at the end of the biological day, and this, in combination with a high homeostatic sleep drive, leads to sleep onset. Figure adapted from Blatter & Cajochen, 2007.

1.3.3.2 An in-depth look at process S

Process S, or the need for sleep, is a homeostatic pressure that accumulates with time awake and dissipates during sleep (Fuller et al., 2006). Physiologically, this homeostatic pressure can be measured during wakefulness through theta/low frequency alpha (5.25-9 Hz) activity (Aeschbach et al., 2001) or indirectly during NREM sleep through EEG delta power, as both these markers increase with extended wakefulness (Achermann et al., 1993). While the mechanisms underlying the sleep homeostat are not fully understood, it has been proposed that the propensity to sleep is associated with sleep factor(s) or somnogen(s) that accumulate during wakefulness until a threshold is reached that facilitates the transition to sleep via inhibition of neuronal activity, and which dissipate during sleep (Porkka-Heiskanen & Kalinchuk, 2011). Following these criteria, a number of endogenous, neuronal activity-dependent metabolites have been proposed as likely candidates, including adenosine (AD), prostaglandin D2 (PGD2), the
cytokines interleukin-I beta (IL-1β) and tumor necrosis factor alpha (TNFα), and the gaseous neurotransmitter nitrous oxide (NO) (Datta, 2010). Among these sleep factors, AD has received the most attention, perhaps because, as Porkka-Heiskanen & Kalinchuk (2011) note, the ability to directly affect neuronal activity is strongest for AD.

AD is a small, ubiquitous nucleoside which, among other roles, it is postulated to play a key role in the monitoring and restoration of energy balance. As a building block for AD tri-, di-, and monophosphates (ATP, ADP, and AMP), AD is directly linked to the energy metabolism of cells and one of the major pathways by which it is formed is through cleavage of the phosphate group from AMP, which is in turn a by-product of the major cellular energy molecule ATP (Scharf et al., 2008; Porkka-Heiskanen & Kalinchuk, 2011). Since AD levels increase as ATP is degraded, increasing AD levels are postulated to reflect a net decrease in the availability of energy stores, that serves to monitor cellular energy balance. Accordingly, studies have shown that AD levels increase steadily in the basal forebrain, cortex, thalamus, and preoptic area (POA) of the hypothalamus as energy stores are depleted during wakefulness; and exponentially in the basal forebrain and thalamus following sleep deprivation (Porkka-Heiskanen et al., 2000). Importantly, AD also appears to play an important role in the restoration of cellular energy stores as increases in extracellular AD levels lead to inhibition of excitatory and inhibitory neurons and, thus, a reduction in cellular energy demands (Cunha, 2005). Of note, the activation of AD receptors (AR) in the basal forebrain, hypothalamus, and pons leads to sleep induction (Porkka-Heiskanen et al., 2011) and, in particular, the activation of AD receptor 1 (AR1) leads to an increase in delta power sleep, suggesting that activation of this signaling pathway is at least one of the mechanism by which changes in cellular metabolism alters sleep homeostasis (Benington et al., 1995; Scharf et al., 2008).

1.3.3.3 An in-depth look at process C

Circadian rhythms – the word circadian derived from the Latin words *circa diem* meaning “about a day” – comprise a number of physiological, biochemical, and neurobehavioural changes that follow a roughly 24 h cycle (Cermakian & Boivin, 2003). Circadian rhythms are generated in the oscillator neurons of the suprachiasmatic nuclei (SCN), which are clusters of neurons positioned on the hypothalamus, above the optic chiasm (Cermakian & Boivin, 2003).
The SCN, which are also referred to as the master or central pacemaker, regulate diurnal behaviours such as sleep and wakefulness, drinking, feeding, attention, and memory (Aloe et al., 2005; Richardson, 2005; Zee & Manthena, 2007).

Circadian regulation of the timing in the switch from sleep to wake and vice-versa is governed by the SCN via monosynaptic and polysynaptic projections of both excitatory and inhibitory natures that extend to the VLPO, as well as to areas implicated in arousal such as the LC and orexinergic neurons in the LH and VMH (Mistlberger, 2005; Saper et al., 2005).

1.3.3.3.1 Generation of circadian rhythms in the master pacemaker

The generation of circadian cycles within the SCN results from the cyclic expression of a number of gene products collectively referred to as clock-controlled genes (CCG) through a feedback loop mechanism that involves regulation at the transcriptional and post-transcriptional levels. Examples of CCGs include period (per) and cryptochrome (cry).

As reviewed by Okamura et al. (2002), Pace-Schott & Hobson (2002), and Richardson (2005), the regulation of per and cry genes is partly under the control of two transcriptional factors: brain and muscle ARNT-like 1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK). At the beginning of the subjective day or circadian time (CT) 0, BMAL1 and CLOCK dimerize and bind to the promoters of per and cry genes, thus activating gene transcription. This results in an increase in the expression of PER and CRY proteins, which in turn dimerize to form PER/PER and PER/CRY dimers that accumulate across the day, reaching maximum levels at the beginning of the biological night (CT12). PER/PER and PER/CRY dimers have inhibitory effects on the transcriptional activity of BMAL1/CLOCK and thus, increased PER and CRY protein expression leads to decreased per and cry gene transcription in this feedback regulatory loop. BMAL1/CLOCK dimers gradually become transcriptionally active again across the night as PER and CRY protein expression reaches a minimum at the end of the biological night (CT 24) due to degradation of remaining undimerized PER and CRY proteins. The transcriptional re-activation of BMAL1/CLOCK coincides with the beginning of the biological day (CT0) and, thus, a new cycle begins (Figure 1.6).
Figure 1.6 Molecular regulation of circadian rhythmicity within neurons of the suprachiasmatic nuclei.

Clockwise from top left panel: The clock-controlled gene products BMAL1 (B) and CLOCK (C) form heterodimers that bind to the gene promoters of period (per) and cryptochrome (cry) in the nucleus. Transcriptional activity of BMAL1 and CLOCK heterodimers is high at CT0 and, thus, the expression of per and cry protein products (PER and CRY, respectively) in the cytoplasm increases rapidly (CT6). As protein concentrations increase, PER and CRY form PER/PER homodimers and PER/CRY heterodimers. These dimers have an inhibitory effect on the transcriptional activity of BMAL1 and CLOCK and, thus, as PER and CRY concentrations increase, the transcription and translation of per and cry genes decreases, coming to a halt by CT12, when maximum levels of PER and CRY are reached. In the absence of gene transcription, protein levels start to decrease, as undimerized PER and CRY proteins in the cytoplasm gradually degrade (CT18). Decrease in the expression of PER and CRY proteins, in turn, leads to gradual disinhibition of BMAL1/CLOCK heterodimers, and re-activation of per and cry genes by BMAL1/CLOCK coincides with the beginning of the biological day (CT0).
As reviewed by Cermakian & Boivin (2003), the diurnal variation in the expression of PER and CRY proteins appears to be at the core of cellular signal transductions responsible for the rhythmicity of SCN neurons, as animal studies using gene knock-out mutations indicate that animals lacking per and cry genes experience a complete loss of circadian rhythmicity. However, while the cyclic expression of PER and CRY proteins is the basis for the rhythmicity of the central pacemaker, there are several inputs and outputs to and from the SCN and, thus, several more levels of feedback regulation of PER and CRY protein expression that collectively give rise to circadian cycles (Cermakian & Boivin, 2003; Saper et al., 2005). Inputs to the SCN in the form of direct neuronal projections, hormones, nutrients, or light can modulate the phase, length, and amplitude of circadian cycles; while outputs from the SCN result in circadian fluctuations in neuronal and physiological functions.

1.3.3.3.2 Light as a modulator of circadian cycles

One of the most important and fascinating properties of the central pacemaker is that properties of the circadian cycle such as its phase, length, and amplitude, can be modified in response to external stimuli or “zeitgebers” via a process referred to as entrainment. Light entrainment is a process by which the sleep-wake cycle and its associated behaviours are phase-shifted in response to changes in environmental light (Onuoha et al., 2000; Gillette & Mitchell, 2002; Buijs et al., 2003; Hofman, 2003; Dardente et al., 2004; Lockinger et al., 2004; Aloes et al., 2005; Richardson, 2005; Reghunandaran & Reghunandaran, 2006). Photic input can result in either a phase-advance or a phase-delay depending on the time of exposure – light exposure in the late biological night and/or early biological morning results in phase-advance, which, in simple terms, means that the subject’s rise time will occur earlier; and light exposure during the late biological day and/or early biological night results in phase-delays, which means that the subject’s sleep onset time will be delayed (Shanahan et al., 1997; Skene, 2003; Yannielli & Harrington, 2004).

Modulation of circadian cycles by light starts in the retina, where a photopigment known as melanopsin renders a small subset of retinal ganglionic cells (RGCs) responsive to light (Hattar et al., 2002) (Figure 1.7). RGC axons project to the olivary pretectal nucleus (OPG), the intergeniculate leaflet (IGL), and the SCN (Hattar et al., 2002). Light stimulation of OPG leads
to the pupillary light reflex, whereas light stimulation of IGL leads to release of mostly neuropeptide Y (NPY) and GABA, which in turn signal to the SCN by way of the geniculohypothalamic tract (GHT) (Dai et al., 1998; Hultborn et al., 1978; Shibata & Moore, 1999). Additionally, direct activation of the SCN occurs via stimulation of the retinohypothalamic tract (RHT), a bundle of nerves that run from the retina directly to the SCN, that relays signals mostly through glutamate and pituitary adenylyl cyclase activating peptide (PACAP) (Zee & Manthena, 2007).

Figure 1.7 Modulation of circadian cycles by light
Light entrainment starts at the level of the eyes, from where retinal ganglionic cells (RGC) project directly to the suprachiasmatic nuclei (SCN) via the retinohypothalamic tract, and indirectly through the intergeniculate leaflet (IGL), which in turn projects to the SCN via the geniculohypothalamic tract.

Entrainment is crucial for the adaptability of organisms to their changing environments and, specifically, light entrainment is important for synchronization of the pacemaker to the day-night cycles (Meijer et al., 2007; Cajochen et al., 2010). Without light entrainment, the longer phase of endogenously generated circadian cycles (a little longer than 24 hrs.) would be out of sync with the day-night cycles, periodically resulting in episodes of sleep during the daytime and wakefulness during the nighttime. From an evolutionary standpoint, light entrainment has been crucial in enabling organisms with circadian rhythms to adjust their behaviours – which include not only sleep and wakefulness, but also alertness, feeding, drinking (Aloe et al., 2005;
Richardson, 2005; Zee & Manthena, 2007), and even reproductive cycles (Elliott, 1976; Bayarri et al., 2009) – to the changes in environmental light associated with seasonal variation.

1.3.3.3 Melatonin – a marker of circadian phase

Melatonin is a hormone involved in the circadian regulation of sleep-wake cycles (Cajochen et al., 2003). The biosynthesis of melatonin involves a number of steps (Figure 1.8). First, tryptophan is hydroxylated by tryptophan hydroxylase to produce 5-hydroxytryptophan (5-HTP), which is then decarboxylated by aromatic amino acid decarboxylase to produce 5-hydroxytryptamine (5-HT), also known as serotonin (Turner et al., 2006). Next, an acetyl group is transferred to serotonin by arylalkylamine N-acetyltransferase (AANAT) to produce N-acetylserotonin, which is then converted into melatonin by hydroxyindole-O-methyltransferase (HIOMT) (Ganguly et al., 2002).

![Figure 1.8 Biosynthesis of melatonin. Figure adapted from Aksnes, 2012. Abbreviations: AAAD – aromatic amino acid decarboxylate; AANAT – arylalkylamine N-acetyltransferase; HIOMT – hydroxyindole-O-methyltransferase; TH – tryptophan hydroxylase]
The synthesis and secretion of melatonin is regulated by the SCN and, as a result, melatonin expression follows a circadian pattern, with plasma concentration peaking during the dark phase of the cycle.

The circadian regulation of melatonin involves polysynaptic connections that extend from the SCN to the pineal gland. During the dark phase of the cycle, the paraventricular nucleus (PVN) activates pre-ganglionic cells in the intermediolateral cell column of the spinal cord, which promote the release of NE from cells in the superior cervical ganglia that project to the pineal gland secretion (Buijs et al., 2003). Activation of $\beta_1$-adrenergic receptors in the pinealocytes results in protein kinase A (PKA) activation and, subsequently, an increase in the enzymatic activity of AANAT (Figure 1.9a) (Buijs et al., 2003). In the presence of light, however, nerve endings of the RHT release glutamate to the SCN, which in turn activate the release of GABA from SCN neurons that innervate the PVN, thus putting a stop to synthesis and secretion of melatonin by inhibiting PVN and its downstream effects on AANAT enzymatic activity (Figure 1.9b) (Major et al., 2003).

Figure 1.9 Production of melatonin during the dark and light phases.
(a) During the dark phase, the paraventricular nucleus (PVN) projects to pre-ganglionic cells in the intermediolateral cell column of the spinal cord, which promote the release of norepinephrine from the superior cervical ganglia onto the pineal gland, resulting in increased synthesis and secretion of melatonin. (b) In the presence of light, neurons within the suprachiasmatic nuclei (SCN) release gamma-aminobutyric acid (GABA) onto the PVN, effectively shutting down activation of PVN and its downstream effects and, thus, inhibiting the synthesis and secretion of melatonin.
The expression of melatonin closely matches changes in environmental light - dim lighting leads to a rise in plasma concentrations of melatonin, while exposure to light results in an immediate drop in plasma melatonin (Ganguly et al., 2002; Buijs et al., 2003; Zee & Manthena, 2007). As a result, fluctuations in the expression of melatonin are directly related to the SCN circadian phase as it entrains to light and, as such, melatonin is an excellent marker of circadian phase.

Melatonin has multiple roles in the circadian regulation of sleep-wake cycles, as it attenuates the wake-promoting signals of the SCN, while promoting the consolidation of sleep (Skene, 2003; Lewy, 2007). One of the mechanisms by which melatonin promotes sleep consolidation is by mediating distal skin vasodilation, which results in drops in core body temperature (CBT) (Kräuchi et al., 1999; Cajochen et al., 2003). This is important because CBT fluctuates diurnally and, in humans, drops in CBT precede sleep onset (Kräuchi et al., 1994). Although the mechanisms underlying the integration of temperature and sleep-wake regulation are not well understood, the preoptic area and anterior hypothalamus (PoAH) have been proposed to be important sites, not only because the firing rate of these neurons increases prior to sleep onset and with warming of peripheral skin – a phenomenon that is seen when skin blood flow and vasodilation increase; but also because PoAH neurons affect the firing rate of brain areas known to regulate sleep wakefulness, such as the posterior hypothalamus, BF, and the dRN (Gilbert et al., 2004).

Melatonin is also believed to affect sleep architecture by manipulating changes in SCN firing rates from REM to NREM sleep, and administration of exogenous melatonin 4-5 hours prior to sleep onset has been widely reported to increase the duration of REM sleep episodes (Dijk & Cajochen, 1997).

Ultimately, given its exquisite sensitivity to changes in environmental light, one of the most important functions of melatonin may be in adjusting sleep duration to changes in the ratio of daytime to nighttime associated with seasonal variation. Given its roles in the promotion and duration of sleep, the phase shifting effects of melatonin have been investigated. Exogenous melatonin administration during the light period (i.e. when endogenous melatonin is not secreted) has phase advancing effects on sleep onset time. This property has made melatonin an attractive candidate for the treatment of sleep disorders, and several studies have documented the efficacy of melatonin in treating circadian sleep disorders such as delayed sleep phase.
syndrome (DSPS) and free-running cycles, and insomnia in elder subjects that display reduced amplitudes of melatonin secretion (Cajochen et al., 2003; Anderson et al., 2008; Pandi-Perumal et al., 2008).

### 1.3.4 Regulation of sleep architecture

#### 1.3.4.1 Transition from wakefulness to NREM

According to the “Reticular Deactivation Theory”, first proposed by Moruzzi (1972), the transition from wakefulness to sleep is a passive process that results from reduction in the tonic activity of the ARAS and, subsequently, activation of the VLPO (Datta, 2010). The transition is mediated by sleep-promoting factors that accumulate during wakefulness, and which initiate processes at the cellular level that eventually result in the manifestation of sleep. As discussed in section 1.3.3.2, AD is among the strongest modulators of neuronal activity.

AD facilitates the transition to sleep by blocking the activation of the ARAS (Datta, 2010) (Figure 1.10). As reviewed by Brown et al. (2012), the sleep-promoting effects of AD are exerted through activation of AR$_1$, which results in pre-synaptic inhibition of neurons that project excitatory inputs to cortical glutamatergic neurons (Greene and Haas, 1991), wake-active cholinergic neurons (Arrigoni et al., 2001; Brambilla et al., 2005; Van Dort et al., 2009), and ORX neurons (Xia et al., 2009); and in post-synaptic inhibition of BF and brainstem cholinergic neurons (Rainnie et al., 1994; Arrigoni et al., 2001; 2006), ORX neurons (Liu & Gao, 2007), hippocampal/neocortical pyramidal neurons (Gerber et al., 1989; McCormick & Williamson, 1989), and thalamo-cortical relay neurons (McCormick, 1992). In addition, activation of the adenosine A$_2$ receptors (AR$_2$) results in activation of the VLPO (Gallopin et al., 2005). The end result is a net decrease in the activity of the ARAS, a net increase in the activity of the VLPO, and subsequently, transition from wakefulness to sleep.
Figure 1.10 Transition from wakefulness to NREM sleep
Adenosine promotes the transition to sleep through activation of adenosine A₁ receptors (AR₁), which results in inhibition (dashed lines) of cholinergic neurons in the brainstem and basal forebrain, orexin neurons, hippocampal/neocortical neurons, and GABAergic neurons projecting to the ventrolateral preoptic nucleus (VLPO); and through activation (solid line) of adenosine A₂ receptors (AR₂), which results in activation of neurons in the VLPO. The net result is a net decrease in the activity of the ascending reticular activating system (ARAS) and a net increase in the activity of the VLPO, and, thus, transition from wakefulness to sleep.

Research over the past three decades suggest that, specifically, the thalamus is a key part of the brain involved in the transition from wakefulness to sleep (Datta, 2010). As reviewed by Datta (2010), the thalamus is composed of two types of neurons: (i) thalamo-cortical relay neurons which relay sensory information from subcortical structures to the cortex, and (ii) thalamo-reticular neurons which act as a gateway that regulates the transfer of sensory information from thalamo-cortical relay neurons to the cortex. During wakefulness, the thalamo-cortical relay neurons are activated and remain in a “ready state” by noradrenergic, serotonergic, and cholinergic inputs from the ARAS in the brainstem (Reviewed by Pace-Schott & Hobson, 2002; Datta, 2010; Brown et al., 2012). However, wakefulness is also associated with the production of neuronal activity-dependent metabolites, as discussed in section 1.3.3.2, and when these accumulate in tandem with hours awake, these metabolites have a dampening effect on noradrenergic, serotonergic, and cholinergic neurons (Datta, 2010; Brown et al., 2012). A reduction in the input of these wake-promoting factors results in decreased activity of thalamo-
cortical relay neurons and increased activity of thalamic reticular neurons, which in turn release GABA onto thalamo-cortical relay neurons, thus hyperpolarizing these neurons and effectively inhibiting the relay of sensory information to the cerebral cortex – a phenomenon that is referred to as sensory gating (Datta, 2010; Brown et al., 2012). Notably, when thalamo-cortical relay neurons reach -65mV, this level of hyperpolarization leads to the activation of special low-threshold calcium channels that generate post-inhibitory rebound spike bursts, which are then transmitted to the cortex, effectively generating the cortical sleep spindles that are characteristic of stage 2 sleep (Steriade et al., 1993; Llinas et al., 2006; Datta 2010; Brown et al., 2012).

1.3.4.2 Transition to SWS

During sensory gating, growth hormone release hormone (GHRH) secreted by clusters of neurons within the hypothalamus (i.e. neurons in the arcuate nucleus and, to a lesser extent, neurons around the ventromedial and periventricular nuclei) (Merchenthaler et al., 1984; Sawchenko et al., 1985; Daikoku et al., 1998; Datta, 2010) activate neurons within the POA, which then release GABA onto components of the ARAS, effectively initiating and maintaining SWS (Gritti et al., 1994; Zardetto-Smith et al., 1995; Steininger et al., 2001; Datta, 2010). SWS is further consolidated by GABAergic interneurons within the cortex, which become active during sleep initiation and which secrete GABA onto cortico-cortical and cortico-thalamic pyramidal cells (Datta, 2010) (Figure 1.11). In a process similar to that involved in the generation of sleep spindles, hyperpolarization of cortico-cortical and cortico-thalamic cells leads to the activation of hyperpolarization-activated, cyclic AMP (cAMP)-modulated cation channels (HCN) and low-threshold calcium channels which in turn result in the delta waves characteristic of SWS (Steriade et al., 1993; Contreras & Steriade, 1995; from Datta, 2010).
Figure 1.11 Transition to SWS
Decreased activity in the ascending reticular activating system (ARAS) leads to decreased activity in thalamo-cortical relay neurons and increased activity in thalamo-reticular neurons, resulting in sensory gating (not shown in the figure – hyperpolarization of thalamo-cortical relay neurons leads to the activation of low-threshold calcium channels that generate post-inhibitory rebound spike bursts, which are then transmitted to the cortex and manifested in the form of the sleep spindles characteristic of stage 2 sleep). While sensory gating is occurring, GABA is released onto components of the ARAS, leading to the initiation and maintenance of SWS; and onto cortico-cortical and cortico-thalamic pyramidal cells (not shown in the figure – hyperpolarization of cortico-cortical and cortico-thalamic cells by GABA leads in the opening of cAMP-modulated cation (HCN) channels, which eventually results in low-threshold spikes and a burst of action potentials. These are manifested in the form of the delta and slow oscillations characteristic of slow-wave sleep).

1.3.4.3 Transition to REM sleep
Perhaps one of the most fascinating and complex aspects of sleep is the generation and maintenance of REM, a stage of sleep that is also referred to as “paradoxical sleep” owing to the presence of cortical EEG patterns similar to those observed in wakefulness during a state of sleep that appears to be deep (Peigneux et al., 2001). REM sleep is characterized by active eye movements, activated EEG cortical patterns, muscle atonia, myoclonic twitches, and significant fluctuations in cardiac and respiratory rhythms and core body temperature (Datta, 2010). Animal studies, where it is possible to measure activity in subcortical structures, also indicate that REM sleep is associated with a theta rhythm in the hippocampus and ponto-geniculo-occipital (PGO) spikes (Morrison et al., 1975; Siegel, 2009).
REM sleep is believed to be regulated by two clusters of neurons: “REM-on neurons”, which become active with the onset of REM sleep, and “REM-off neurons”, which become completely silent during REM sleep. The composite of findings from *in vitro* and *in vivo* studies suggest that REM-on neurons include neurons within the LDT/PPT and the pontine reticular formation (PRF), where cholinergic projections from the LDT/PPT are believed to activate critical areas within the PRF involved in mediating the physiological patterns and characteristics observed in REM sleep (reviewed by McCarley, 2007). On the other hand, REM-off neurons are of an aminergic nature, postulated to be located within areas of the RN, LC, and the anterior pontine tegmentum/midbrain junction (reviewed by McCarley, 2007).

Although the mechanisms underlying the initiation and maintenance of REM sleep are not fully understood, two possible mechanisms have been proposed. One theory, put forward by Lu et al. (2006), proposes that the regulation of REM sleep is mediated by interactions between REM-on and REM-off neurons that are similar to the flip-flop switch mechanism of sleep and wakefulness, where reciprocally inhibitory GABAergic neurons extend from REM-off to REM-on neurons and vice-versa, thereby mediating cycling through NREM and REM sleep (McCarley, 2007). The other theory, first proposed by McCarley & Hobson (1975), is called the Reciprocal Interaction Model and it is significantly more complex. According to this model, as illustrated in figure 1.12, LDT/PPT neurons project excitatory neurons to reticular effector neurons (which in turn project back, providing a positive feedback mechanism), but also to REM-off neurons within the LC and dRN (Jones, 1993; Li et al., 1998; McCarley, 2007). On the other hand, serotonergic neurons in REM-off neurons are believed to inhibit cholinergic neurons in the LDT as well as REM-off neurons within the LC and dRN, thereby providing a inhibitory feedback mechanism (Luebke et al., 1992; McCarley, 2007). The result is that while cholinergic secretion from the LDT/PPT mediates the onset and maintenance of REM sleep through the positive feedback mechanism that it produces with the reticular effector neurons, cholinergic secretion also gradually excites REM-off neurons, which upon full activation inhibit REM-on neurons, thus terminating REM sleep (McCarley, 2007).
Figure 1.12 Regulation of REM sleep.
REM-on neurons are activated through a positive feedback mechanism: excitatory neurons (solid arrows) project from the laterodorsal tegmental (LDT) and pedunculopontine nuclei (LDT) to the effector neurons in the reticular formation and vice-versa, thereby leading to the initiation and maintenance of REM sleep. Excitatory neurons also project from the LDT/PPT to REM-off neurons within the locus coeruleus (LC) and the dorsal raphe nuclei (dRN). As the activity of REM-off neurons increases, inhibitory neurons (dashed arrows) that project from the dRN to REM-on neurons become activated and, eventually, REM sleep is terminated. Of note, inhibitory neurons within the dRN also project back to REM-off neurons and, thus, REM-off neuron activity is regulated through a negative feedback mechanism. Figure adapted from McCarley, 2007.

1.4 Sleep and ADHD

Sleep or sleep-like states are exhibited by a wide array of living organisms, from simple organisms such as fruitflies, zebra fish and roundworms, to members of the mammalian system (Porkka-Heiskanen & Kalinchuk, 2011). Studies have shown that in fruitflies and rats, prolonged sleep deprivation can lead to death, and, in humans, sleep deficiency is associated with higher rates of cardiovascular, metabolic, and mental disorders (Luyster et al., 2012), suggesting that sleep is a fundamental and necessary aspect of life.

Although the specific functions of sleep have not been well elucidated, it has been postulated that sleep has roles in energy conservation, brain thermoregulation, brain detoxification, tissue
restoration, and in the regulation of brain plasticity for memory consolidation and learning (Wang et al., 2011).

Sleep is of particular relevance to ADHD because sleep plays a pivotal role in cognitive function, learning, and memory consolidation (Peigneux et al., 2001; Stickgold et al., 2001; Walker & Stickgold, 2006; Marshall & Born, 2007; Wang et al., 2011); and sleep deprivation or disturbances can result in symptoms varying in severity, from unconscious deficits in cognitive performance to disabling sleepiness and fatigue that noticeably affect cognitive, emotional, and physical function, putatively giving rise to or exacerbating ADHD symptoms (Stickgold et al., 2001; Siegel, 2001; Gross & Goltman, 1999; Oosterloo et al., 2006). Thus, relatively extensive research has been carried out to investigate the link between sleep and ADHD. The following sections, which were first provide a comprehensive account of the research that has been conducted in the area.

1.4.1 Symptoms of ADHD in sleep disorders

Sleep disorders are conditions in which sleep is disturbed and/or abnormal due to difficulties associated with the quality, quantity, and/or stability of sleep (Shapiro et al., 2006). Studies have shown that primary sleep disorders are associated with ADHD–like symptoms. Although whether the nature of such association is causative is unclear, it has been proposed that sleep fragmentation may give rise to ADHD-like symptoms (Pollmacher & Schultz, 1993). Indirectly, sleep deprivation due to sleep fragmentation may lead to excessive daytime sleepiness, which may in turn interfere with sustained attention. Alternatively, direct changes in sleep architecture due to sleep fragmentation may affect daytime processes associated with mood, memory, and learning – all of which are affected in ADHD. Studies in which ADHD-like symptoms were investigated are discussed in the following sections.

1.4.1.1 Hypersomnia

Hypersomnia is the term used to describe excessive daytime sleepiness. Oosterloo et al. (2006) carried out a study comparing adults with ADHD to adults with Excessive Daytime Sleepiness
(EDS) and found that approximately 18% of EDS patients met DSM-IV criteria for ADHD, and, alternatively, that approximately 37% of ADHD patients met criteria for EDS, suggesting a significant degree of overlap between symptoms associated with ADHD and symptoms associated with hypersomnia.

1.4.1.2 **Restless legs syndrome and periodic limb movements in sleep**

Restless legs syndrome (RLS) is a condition in which subjects feel an urge to move the legs due to feelings of pain and discomfort described as “tickles”, “bugs”, “spiders”, and “a lot of energy in the legs” (Picchietti & Picchietti, 2008). This condition is associated with considerable motor restlessness, and approximately 80% of RLS cases are accompanied by Periodic Limb Movement in Sleep (PLMS). PLMS is a condition in which periodic and repetitive limb movements lasting 0.5-5.0 seconds and occurring more than 5 times an hour during sleep significantly affect sleep stability (Montplaisir et al., 1997).

ADHD-like symptoms have been documented in RLS and PLMS. In a retrospective clinical study, 93% of children with RLS met DSM-IV criteria for ADHD (Picchietti & Walters, 1999). Although the high percentage is likely to be the result of recruitment bias, as the clinic at which the study was conducted specializes in ADHD and RLS, other groups have reported associations between ADHD-symptoms and RLS in both children and adults (Chervin et al., 2002b; Wagner et al., 2004; Gaultney et al., 2005).

1.4.1.3 **Sleep disordered breathing**

Sleep Disordered Breathing (SDB) includes conditions such as primary snoring (PS), upper airway resistance syndrome (UARS), and obstructive sleep apneas (OSA) (Downey et al., 1993; Urschitz et al., 2003). Although they are all characterized by snoring, these disorders range in severity. PS, for instance is not associated with intermittent hypoxia, hypercarbia, or sleep disrupting arousals. UARS, on the other hand, is associated with labored breathing and repeated arousals; and OSA is characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction which results in apnea, hypoxia, hypercarbia, and repeated
arousals (Downey et al., 1993; Urschitz et al., 2003; Melendres et al., 2004). Studies have shown that SDB is associated with inattentive and hyperactive behavior in children (Melendres et al., 2003; Gaultney et al., 2005). Children with PS have been shown to suffer from more sleepiness, inattention, and hyperactivity than healthy controls (Ali et al., 1993; 1996; Chervin et al., 2005; Chervin et al., 2002a; O’Brien et al., 2004a; Urschitz et al., 2003). Also, children with OSA reportedly have problems with sustained attention and verbal skills, while adults with OSA have attention problems (Lewin et al., 2002; Mazza et al., 2005). While these studies support an association between SDB and ADHD-like symptoms, O’Brien et al. (2004b) observed that while children with SDB had lower attention and executive function, no differences in ADHD-associated behaviours as measured by the Conners’ Parent Rating Scale and Child Behavior Checklist were found between children with SDB and healthy controls. Moreover, Chervin & Archbold (2001) reported that while there are no associations between hyperactivity and SDB, there was an association between PLMS scores and hyperactive behavior when children had SDB, suggesting an inter-relationship between SDB, PLMS, and hyperactive behavior.

1.4.2 Sleep disorders in ADHD

In this section, studies on the manifestation of sleep disturbances/disorders in patients with ADHD are discussed.

1.4.2.1 Sleep quality and sleep architecture

The majority of studies investigating sleep in ADHD have been conducted in child populations, primarily because the notion that ADHD persists into adulthood is fairly new (Doyle, 2004; McGough & Barkley, 2004). In studies using subjective methodologies, all but three studies (Corkum et al., 1999; Mick et al., 2000; Stein et al., 2000) reported sleep problems in children with ADHD, including initial and middle insomnia, nocturnal awakenings, snoring, breathing problems, restless sleep, parasomnias, nightmares, short sleep time, daytime sleepiness, and anxiety around bedtime (Ball et al., 1997; Chervin et al., 1997; Marcotte et al., 1998; Ring et al.,
1998; Owens et al., 2000; LeBourgeois et al., 2004; Gau, 2006; Lim et al., 2008; Sung et al., 2008; Hvolby et al., 2009; Li et al., 2009; Mayes et al., 2009) (Table 1.4).

The use of objective methods such as actigraphy and polysomnography (PSG) for the assessment of sleep in children with ADHD has resulted in variable findings (Table 1.5). Increases in sleep onset latency (Hvolby et al., 2008; van der Heijden et al., 2005), daytime sleepiness (Palm et al., 1992; Golan et al., 2004), and REM sleep latency (Busby et al., 1981; Palm et al., 1992; O’Brien et al., 2003a; 2003b) have been reported; and there have been controversies as to whether there are increases or decreases in REM sleep percentage (O’Brien et al., 2003a; 2003b; Golan et al., 2004; Kirov et al., 2004; Gruber et al., 2009; Silvestri et al., 2009), or total sleep time (Kirov et al., 2004; Miano et al., 2006; Gruber et al., 2009; Owens et al., 2009) in children with ADHD. In contrast, some studies found no abnormalities in sleep by actigraphy (Corkum et al., 2001; Wiggs et al., 2005) or PSG (Crabtree et al., 2003; Sangal et al., 2005) in children with ADHD. Interestingly, two studies reported increased variability in the standard deviations of sleep variables such as total sleep time and sleep onset time in children with ADHD, suggesting that sleep in these children is characterized by marked night-to-night instability (Gruber et al., 2000; Gruber & Sadeh, 2004).
Table 1.4 Studies of sleep in children with ADHD by subjective methodologies.
Adapted and updated from Yoon et al., 2012. See appendix I for complete table and further information such as study sample sizes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball et al., 1997</td>
<td>More sleep problems and night awakenings in medicated ADHD children than in controls. No significant differences between medicated and non-medicated children in reports of sleep problems.</td>
</tr>
<tr>
<td>Chervin et al., 1997</td>
<td>ADHD children had more habitual snoring than psychiatric controls and healthy controls.</td>
</tr>
<tr>
<td>Marcotte et al., 1998</td>
<td>Children with ADHD and/or LD scored higher on the Sleep and Breathing Problems Scale and the Sleepiness Scale.</td>
</tr>
<tr>
<td>Ring et al., 1998</td>
<td>Although the mean duration of sleep in ADHD children and their siblings did not differ significantly, ADHD children had higher rates of initial and middle insomnia, nocturnal enuresis, and sleepwalking.</td>
</tr>
<tr>
<td>Corkum et al., 1999</td>
<td>Dyssomnias and involuntary movements during sleep were more strongly associated with medication status, co-morbidity with ODD, and separation anxiety than with ADHD diagnosis.</td>
</tr>
<tr>
<td>Mick et al., 2000</td>
<td>Although sleep difficulties were associated with ADHD, regression analysis revealed that such difficulties were associated with the use of stimulant medication and co-morbidity with anxiety disorder.</td>
</tr>
<tr>
<td>Owens et al., 2000</td>
<td>Children with ADHD had increased rates of bedtime resistance, sleep onset delays, night awakenings, parasomnias, and daytime sleepiness; and decreased sleep duration.</td>
</tr>
<tr>
<td>Stein et al., 2002</td>
<td>Medicated adolescents with ADHD had more sleep disturbances than non-medicated adolescents with ADHD and controls. Sleep disturbances in medicated adolescents were associated with depression, rather than with ADHD diagnosis. In the non-medicated group, sleep disturbances were associated with anxiety.</td>
</tr>
<tr>
<td>LeBourgeois et al., 2004</td>
<td>Compared to healthy controls, a higher percentage of children with ADHD suffered from daytime sleepiness, poor sleep quality, initial insomnia, and trouble waking up in the morning compared to controls. Among subtypes, ADHD-HI children snored more and had a tendency towards more trouble going to bed than their ADHD-C counterparts.</td>
</tr>
<tr>
<td>Gau et al., 2006</td>
<td>Sleep problems such as dyssomnia, parasomnia, SDB, and daytime inadvertent naps were more frequent in children with more severe symptoms of ADHD.</td>
</tr>
<tr>
<td>Lim et al., 2008</td>
<td>Children with ADHD were reported to sleep less than healthy controls.</td>
</tr>
<tr>
<td>Sung et al., 2008</td>
<td>About 30% of children with ADHD had mild sleep problems and about 45% had moderate to severe sleep problems such as trouble falling asleep, bedtime resistance, difficulty getting up, night awakenings, restless sleep, breathing difficulty during sleep, and tiredness on waking.</td>
</tr>
<tr>
<td>Hvolby et al., 2009</td>
<td>More sleep problems such as bedtime resistance, difficulty falling asleep, increased sleep onset latency, restless sleep, sleep talking, teeth grinding, nightmares, and difficulty waking in the morning in children with ADHD than in clinical controls and healthy controls.</td>
</tr>
<tr>
<td>Li et al., 2009</td>
<td>A multiple regression model controlled for age, gender, and medication status revealed that history of ADHD correlated significantly with sleep problems such as bedtime resistance, sleep onset delay, sleep anxiety, night awakenings, parasomnia, SDB, and daytime sleepiness.</td>
</tr>
<tr>
<td>Mayes et al., 2009</td>
<td>While ADHD-I children did not differ from controls, ADHD-C children had more sleep problems than ADHD-I (trouble falling asleep, restless sleep, night awakenings) and control children (trouble falling asleep, sleeping less than normal). Also, ADHD-I children had more reports of daytime sleepiness. In both the ADHD-I and ADHD-C groups, co-morbidity with anxiety or depression was associated with greater sleep problems (trouble falling asleep, restless sleep, night awakenings, sleep walking/talking, early rise, and reduced sleep time). In all the children in the study, ADHD symptom severity correlated with sleep problem scores.</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD-C – ADHD of the combined subtype; ADHD-H/I – ADHD of the hyperactive/impulsive subtype; ADHD-I – ADHD of the inattentive subtype; LD – learning disability; ODD – oppositional defiant disorder; SDB – sleep disordered breathing
Table 1.5 Studies of sleep in children with ADHD by objective methodologies.  
Adapted and updated from Yoon et al., 2012. See appendix II for complete table and further information.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busby et al., 1981</td>
<td>PSG indicated increased REM sleep latency in hyperkinetic group.</td>
</tr>
<tr>
<td>Palm et al., 1992</td>
<td>PSG indicated that children with deficits in attention, motor control and perception had increased TSP, REM percentage, SOL, and REM sleep latency; and decreased stage 1 sleep percentage.</td>
</tr>
<tr>
<td>Gruber et al., 2000</td>
<td>Actigraphy indicated that while there were no significant differences on SOT, sleep duration, or true sleep between ADHD and control groups, the standard deviations of these parameters were significantly different between groups, suggesting increased night to night variability in ADHD.</td>
</tr>
<tr>
<td>Corkum et al., 2001</td>
<td>Actigraphy indicated no significant differences between ADHD and healthy controls.</td>
</tr>
<tr>
<td>Konofal et al., 2001</td>
<td>PSG and video recording indicated no significant differences between ADHD children and controls, although video recordings revealed more limb movements in ADHD children.</td>
</tr>
<tr>
<td>Crabtree et al., 2003</td>
<td>PSG indicated that in ADHD children, 7% had SDB, 36% had PLMI&gt;5, and 6% had sleep fragmentation. Actigraphy indicated significant night to night variability.</td>
</tr>
<tr>
<td>O’Brien et al., 2003a</td>
<td>PSG indicated that children with significant ADHD symptoms had increased REM sleep latency and decreased REM sleep percentage compared to controls.</td>
</tr>
<tr>
<td>O’Brien et al., 2003b</td>
<td>PSG indicated increased REM sleep latency and decreased REM sleep percentage in clinical and community samples of ADHD; and increased SWS and PLMI, and decreased spontaneous arousal index in clinical samples of ADHD compared to healthy controls.</td>
</tr>
<tr>
<td>O’Brien et al., 2003c</td>
<td>PSG indicated decreased REM sleep percentage in ADHD children, and reduced TST in medicated ADHD children.</td>
</tr>
<tr>
<td>Golan et al., 2004</td>
<td>PSG indicated increased REM sleep percentage, arousal index, RDI, number of children with SDB, and number of children with PLMS, and sleepiness in ADHD.</td>
</tr>
<tr>
<td>Gruber &amp; Sadeh, 2004</td>
<td>Actigraphy indicated higher night-to-night variability in variables such as sleep onset time, TST, and true sleep time in ADHD.</td>
</tr>
<tr>
<td>Huang et al., 2004</td>
<td>PSG indicated increased stage 3 sleep percentage and AHI, and decreased mean saturated O2; as well as higher prevalences of SDB and PLMI&gt;5 in children with ADHD.</td>
</tr>
<tr>
<td>Kirov et al., 2004</td>
<td>PSG indicated time in bed, TST, REM sleep time, number of sleep cycles, and short movement-related epochs.</td>
</tr>
<tr>
<td>Sangal et al., 2005</td>
<td>PSG indicated that values were within the normal range in sleep variables.</td>
</tr>
<tr>
<td>Wiggs et al., 2005</td>
<td>Actigraphy indicated no significant differences between ADHD subtypes.</td>
</tr>
<tr>
<td>Miano et al., 2006</td>
<td>PSG indicated decreased time spent in bed, sleep period time, TST; and increased stage shifts. Also, decreases in CAP rate were found in stage 2 of NREM sleep.</td>
</tr>
<tr>
<td>Silvestri et al., 2007</td>
<td>PSG indicated increased prevalence of ictal and enterictal epileptiform discharges, RLS, sleep related movement disorders, arousals, and SDB in ADHD.</td>
</tr>
<tr>
<td>Hvolvy et al., 2008</td>
<td>Actigraphy indicated higher SOL in ADHD children than in psychiatric and healthy controls.</td>
</tr>
<tr>
<td>Goraya et al., 2009</td>
<td>PSG indicated increased arousal index, wake after sleep onset, and daytime sleepiness; and decreased sleep efficiency ADHD. Also, 64% of children with ADHD met criteria for SDB.</td>
</tr>
<tr>
<td>Gruber et al., 2009</td>
<td>PSG indicated decreased TST and REM percentage in ADHD. According to parental reports, children with ADHD had more sleep onset delays and anxiety compared to controls.</td>
</tr>
<tr>
<td>Owens et al., 2009</td>
<td>Actigraphy indicated that although ADHD and controls did not differ in TST, ADHD children had decreased real sleep time, likely due to more interruptions during sleep.</td>
</tr>
<tr>
<td>Silvestri et al., 2009</td>
<td>PSG indicated that compared to controls, ADHD children had decreased TST, SE, and REM sleep; and increased stage 3 NREM sleep, arousal index, and REM latency. When data were stratified into ADHD-I and ADHD-HI/C, PLMI was higher in ADHD-HI/C children.</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD-C – ADHD of the combined subtype; ADHD-H/I – ADHD of the hyperactive/impulsive subtype; ADHD-I – ADHD of the inattentive subtype; PLMI – periodic limb movement index; PLMS – periodic limb movements in sleep; PSG – polysomnography; RDI – respiratory disturbance index; REM – rapid eye movement; RLS – restless legs syndrome; SDB – sleep disordered breathing; SE – sleep efficiency; SOL – sleep onset latency; SOT – sleep onset time; SWS – slow wave sleep; TSP – total sleep period; TST – total sleep time.
Regarding the adult population, studies indicate that adults with ADHD report subjective sleep problems such as non-restorative, poor sleep quality (Schredl et al., 2007), initial/middle insomnia (Surman, 2006; Gau et al., 2007; Schredl et al., 2007), restless sleep (Schredlt et al., 2007; Surman, 2006) and daytime sleepiness (Oosterloo et al., 2006; Sowell et al., 2003) (Table 1.6).

### Table 1.6 Studies of sleep in adults with ADHD by subjective methodologies.
Adapted and updated from Yoon et al., 2012. See appendix III for complete table and further information such as study sample sizes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangal &amp; Sangal, 2004</td>
<td>ADHD subjects had a significantly lower ESS score than sleep disordered subjects. With a mean score of 8.3, ADHD subjects did not meet criteria for EDS. ESS score did not correlate with inattention or hyperactivity/impulsiveness scores in ADHD subjects.</td>
</tr>
<tr>
<td>Oosterloo et al., 2006</td>
<td>Approximately 38% of ADHD patients met criteria for excessive daytime sleepiness (EDS), compared to 96% in HI patients.</td>
</tr>
<tr>
<td>Gau et al., 2007</td>
<td>ADHD-I group: Differences reported in sleep need and number of sleep problems between ADHD, probable-ADHD and non-ADHD subgroups, with ADHD subgroup having the highest number of needed sleep hours and sleep problems, both current and lifetime. Significant sleep problems in ADHD and probable-ADHD subgroups included early and middle insomnia, sleep talking, nightmares, and snoring. ADHD-H/I group: Differences reported in the number of sleep problems between ADHD, probable-ADHD, and non-ADHD subgroups, with ADHD subgroup having the highest number of sleep problems, both current and lifetime. Significant sleep problems in ADHD and probable-ADHD subgroups included early insomnia, sleep terrors, and snoring.</td>
</tr>
<tr>
<td>Schredl et al., 2007</td>
<td>In comparison to controls, ADHD subjects had lower sleep quality, un-refreshing sleep, insomnia, increased SOL and nocturnal awakenings, problems with sleep quality and sleep/wake patterns, nocturnal breathing disorders, parasomnias, movement disorders, and felt more tired during the day. Of note, movement disorders, insomnia, problems with sleep quality and sleep/wake disorders, parasomnias, and tiredness during the day were found to be associated with depression scales, rather than with ADHD scales; while co-morbidity with depression appeared to be associated with insomnia, poor sleep quality, and feeling un-refreshed in the morning. Medication status did not appear to affect the presence or severity of sleep problems.</td>
</tr>
<tr>
<td>Surman et al., 2008</td>
<td>Compared to controls, ADHD subjects had more difficulties going to sleep, waking up in the morning, restless sleep, sleep talking, nightmares, and repetitive actions in sleep; and increases in sleep latency, nocturnal awakenings, and daytime sleepiness. Controlling for medication status and co-morbidities, it was found that the associations between ADHD and sleep disturbances still hold.</td>
</tr>
<tr>
<td>Caci et al., 2009</td>
<td>A negative association was found between scores for the Composite Scale of Morningness (CSM) and inattention in the Adult Self Report Scale (ASRS), suggesting that there may be ADHD subtype differences with respect to circadian preference, with the inattentive subtype being more of an evening type.</td>
</tr>
</tbody>
</table>

As with childhood ADHD, objective methodologies have yielded inconsistent findings in adult ADHD: while one group reported no difference between ADHD subjects and controls (Philipsen et al., 2005), others have reported increased movement index (Kooij et al., 2001), and decreases in sleep onset latency (Boonstra et al., 2007), sleep efficiency (Boonstra et al., 2007; Sobanski et al., 2008a) and REM sleep percentage (Sobanski et al., 2008a) (Table 1.7).

**Table 1.7 Studies of sleep in adults with ADHD by objective methodologies.**
Adapted and updated from Yoon et al., 2012. See appendix IV for complete table and further information such as study sample sizes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Kooij et al., 2001</em></td>
<td>Actigraphy indicated that at baseline, ADHD subjects had poorer sleep quality and increased activity level and movement index in comparison to controls. After three weeks of medication, sleep quality improved, and movement index decreased in ADHD subjects.</td>
</tr>
<tr>
<td><em>Phillipsen et al., 2005</em></td>
<td>PSG indicated no differences between ADHD and control subjects. Subjectively, adults with ADHD reported poorer sleep quality, lower restorative value of sleep, worse mood in the evening, and more fatigue and psychosomatic symptoms during sleep onset.</td>
</tr>
<tr>
<td><em>Boonstra et al., 2007</em></td>
<td>Actigraphy indicated that ADHD subjects had lower SE and increased SOL compared to controls. Effects of MPH treatment included decreases in nocturnal awakenings, time in bed, actual sleep, increased sleep onset latency; and delayed sleep bedtime. Correlation tests revealed no associations between co-morbidities and sleep variables.</td>
</tr>
<tr>
<td><em>Sobanski et al., 2008a</em></td>
<td>PSG indicated that in comparison to controls, all ADHD subjects had decreased SE and REM sleep; and increased nocturnal awakenings and stage 1 sleep percentage. ADHD subjects free of co-morbidities exhibited lowered SE, duration of first REM sleep period, and REM sleep percentage; and higher nocturnal awakenings and percentage of sleep in the wake state were reported. After a four-week treatment with MPH, ADHD subjects showed improvements in SE and decreased SOL.</td>
</tr>
</tbody>
</table>

Abbreviations: MPH – methylphenidate; REM – rapid eye movement; SE – sleep efficiency; SOL – sleep onset latency

It should be noted that while reports that stimulant medications affect sleep latency, sleep quality, and total sleep time (Corkum et al., 1999; Mick et al., 2000; Stein et al., 2002; Schwartz et al., 2004; Corkum et al., 2008) can underestimate the results of some of the studies (Chervin et al., 1997; Crabtree et al., 2003; O’Brien et al., 2003a; 2003b; LeBourgeois et al., 2004; Sangal & Sangal, 2004; Gau, 2006; Oosterloo et al., 2006; Gau et al., 2007; Lim et al., 2008; Sung et al., 2008; Caci et al., 2009; Goraya et al., 2009; Silvestri et al., 2009) discussed in this section, well-controlled studies have demonstrated that sleep problems exist in medication-free ADHD patients (Bau et al., 1997; Gruber et al., 2000; Owens et al., 2000; Kooij et al., 2001; Gruber & Sadeh, 2004; Kirov et al., 2004; van der Heijden et al., 2005; Miano et al., 2006; Surman, 2006; Schredel et al., 2007; Hvolby et al., 2008; Sobanski et al., 2008a; Li et al., 2009; Mayes et al.,
2009; Owens et al., 2009), which suggests that sleep disorders are not exclusively associated with the use of stimulant medication. Moreover, there have been reports of improvements in sleep quality in medicated ADHD patients (Kooij et al., 2001; Sobanski et al., 2008a).

1.4.2.2 Periodic limb movements in sleep

A number of studies have provided evidence to suggest an association between RLS/PLMS and ADHD in children. While two studies reported no difference in the frequency of periodic limb movements in ADHD and healthy controls (Chervin et al., 1997; Sangal et al., 2005), five studies reported more frequent RLS and/or PLMS in ADHD (Konofal et al., 2001; Golan et al., 2004; Picchietti et al., 1998; 1999; Oner et al., 2007). In the adult population, there is only one published study reporting increased frequency of RLS in ADHD (Zak et al., 2009).

Although the mechanisms underlying the high rates of PLMS/RLS and ADHD co-morbidity are not well understood, some proposals have been put forward. Initial interest in RLS and ADHD co-morbidity developed because the two disorders are characterized by DA deficiency in some individuals. The nature of the deficit, however, differs between the two disorders. In RLS, dopaminergic deficiency is caused by inadequate dopamine synthesis, evidenced by the effectiveness of dopamine precursor L-Dopa and dopamine receptor agonists in ameliorating the symptoms of the disorder (Ondo et al., 2004). In ADHD, dopaminergic deficiency is believed to be caused by increased clearance of the neurotransmitter and abnormal signaling of the dopamine receptor. This is supported by the observed effectiveness of drugs such as methylphenidate and dextro-amphetamine, both of which act by inhibiting the re-uptake of dopamine, thus prolonging the time that dopamine remains at the synapse (Volkow et al., 2002).

Recently, some groups have focused on iron, as it affects both dopamine synthesis and dopaminergic signaling. Both RLS/PLMS and ADHD have been reported to be associated with lower ferritin levels (Konofal et al., 2007; Oner et al., 2007). Ferritin is a protein that carries iron in the cell, and thus, it is a measure of intracellular iron levels (Octave et al., 1983). Low iron levels may result in reduced dopamine synthesis and abnormal dopaminergic signaling, thus resulting in RLS/PLMS and ADHD comorbidity (Konofal et al., 2007; Oner et al., 2007). In line with this hypothesis, it has been reported that ADHD children with low serum ferritin levels
(<45µg/l) present with more severe ADHD symptoms and problems with sleep-wake transitions (Cortese et al., 2009). Moreover, iron supplementation reportedly results in significant improvement in ADHD symptoms (Konofal et al., 2008).

1.4.2.3 Sleep disordered breathing

There is evidence of an association between SDB and childhood ADHD. Compared to healthy controls, children with ADHD reportedly have more habitual snoring (Chervin et al., 1997), raised apnea hypopnea index (AHI) (Huang et al., 2004), and raised respiratory disturbance index (RDI) (Golan et al., 2004) values. It should be noted that, while snoring has been reported in young adults with ADHD (Gau et al., 2007), SDB has not been objectively assessed in adult ADHD.

1.4.2.4 Circadian sleep disorders

There is evidence to suggest a clinically significant association between circadian sleep disorders and ADHD. As discussed in section 1.4.2.1, studies have shown that initial insomnia is common in ADHD, and it has been reported that a later circadian preference (eveningness) is associated with ADHD-like deficits (Rybak et al., 2007; Caci et al., 2009; Bae et al., 2010), while morning bright light – which has phase advancing effects and improves seasonal mood symptoms – improves neuropsychological symptoms of ADHD and depression (Rybak et al., 2006). Moreover, phase delays in ADHD subjects with sleep-onset insomnia have been confirmed in studies measuring the secretion of melatonin using the dim light melatonin onset (DLMO) test, which is among the most reliable markers of the human circadian system (Lewy et al., 1999): in a study of children with ADHD (Van der Heijden et al., 2005), DLMO was reported to occur significantly later in children with sleep-onset insomnia (20:32 ± 00:55 hrs, n = 78) than in children without sleep-onset insomnia (19:47 ± 00:49 hrs, n = 30); and in a study of adults with ADHD (Van Veen et al., 2010), DLMO was reported to occur significantly later in adults with sleep-onset insomnia (23:15 ± 01:19 hrs, n = 26) than in adults without sleep-onset insomnia (22:00 ± 00:54 hrs, n = 8). Finally, the existence of circadian problems in ADHD has been shown in molecular studies, as ADHD has been reported to be associated with
altered expression levels of BMAL1 and PER1 proteins (Baird et al., 2012), as well as polymorphisms in the *clock* gene (Kissling et al., 2008; Xu et al., 2010). Altogether, these studies provide evidence to suggest that some of the sleep difficulties in ADHD may be associated with abnormalities in the regulation of circadian cycles.

1.4.3 **Elucidating neurological mechanisms underlying ADHD pathology through assessment of sleep**

The studies discussed in the previous sections provide evidence that patients with sleep disorders can display ADHD-like symptoms and, alternatively, that patients with ADHD can suffer from sleep disturbances characteristic of sleep disorders. The high degree of overlap in symptoms associated with ADHD and symptoms associated with sleep disorders can potentially lead to issues of misdiagnosis because the similarity in the presentation of symptoms can make it difficult to discriminate one condition from the other. Thus, some have argued that sleep disturbances are not intrinsic to ADHD, but rather the result of an underlying sleep disorder. For instance, in PLMS and RLS, sleep fragmentation resulting from multiple arousals during sleep can lead to excessive daytime sleepiness, and, in turn, excessive daytime sleepiness can lead to inattention and behavioural problems such as hyperactivity and impulsivity, which may be misdiagnosed as ADHD (Goll and Shapiro, 2006). Indeed, misdiagnosis of sleep disorders for ADHD have previously been documented: Walters et al. (2000) reported that out of 7 children with ADHD and co-morbid RLS, 3 no longer met criteria for ADHD after RLS was treated; Goll and Shapiro (2006) described a case study in which treatment of RLS led to attenuation of restlessness and problems with inattention; and Huang et al. (2007) reported that in ADHD children with mild OSA (1 > AHI > 5), tonsillectomy led to more improvements in attention span and impulse control than treatment with MPH. Also, studies have shown that adenoidecetomy and tonsillectomy in children with obstructive breathing problems in sleep result in significant improvements on measures of attention and behavioural problems such as aggression and hyperactivity (Avior et al., 2004; Dillon et al., 2007), and a case study of a misdiagnosis of OSA for adult ADHD has been described (Naseem et al., 2001).

While the overlap of symptoms in sleep disorders and in ADHD may give rise to problems with misdiagnosis; it also highlights the importance of sleep in ADHD, and the possibility that
common mechanisms may exist, that give rise to both sleep disturbances and symptoms of ADHD. However, the nature of the relationship between sleep and ADHD is not well understood.

In both childhood and adult studies, the fact that different groups reported different sleep disturbances has made the understanding of the relationship between sleep disorders and ADHD difficult. In studies of childhood ADHD, the discordance is likely to be partly due to flaws in research methodology. Factors related to statistical power, differences in inclusion/exclusion criteria, differences in subjective (different questionnaires) and objective (actigraphy versus PSG) methods used, the number of nights of recordings, and unsatisfactory control of confounding variables such as co-morbidity, medication-status, and first-night effects – a phenomenon associated with PSG, in which the use of numerous electrodes and wires creates an unfamiliar sleep environment that has a distorting effect on the first night of recordings (Riedel et al., 2001) – have made it difficult to make comparisons between studies (Corkum et al., 1998; Mick et al., 2000; Sadeh et al., 2006; Cortese et al., 2009; Owens et al., 2009).

Specific to the adult population, the paucity of published data has been a central issue. While insomnia, changes in sleep architecture, excessive daytime sleepiness, PLMS, SDB, and DSPS have been reported in children with ADHD, it is unclear whether there are similar sleep problems in adults. If the reports of childhood ADHD are any indication, however, adult ADHD is expected to be associated with as much diversity in the reports of sleep disturbances/disorders as childhood ADHD.

The diversity of reports, however, also reflects the complexity of ADHD. That ADHD is associated with multiple sleep disturbances, multiple co-morbidities, and multiple symptoms suggests that ADHD may in fact encompass a number of disorders. Just as ADHD, CD, and ODD were once lumped together under the rubric of “moral imbecility”, perhaps ADHD, as we know it today, is the composite of related disorders. Disorders such as insomnia, excessive daytime sleepiness, RLS, OSA, and DSPS have been reported in ADHD; with proposed etiological factors related to iron deficiencies, abnormal cortex arousal regulation, and abnormal circadian cycles (reviewed by Yoon et al., 2012). The underlying mechanisms that drive an ADHD patient to develop one sleep disorder over another are not known, and the occurrence of these sleep disorders appears to be random. This seemingly random occurrence of sleep
disorders, however, may be the result of failure to stratify the group. In other words, while ADHD as a whole is a complex disorder with multiple associated co-morbidities and symptoms, there may be subgroups within the disorder that share commonalities.

1.5 Rationale and research goals

In adults, ADHD presents as ADHD-I or ADHD-C. As discussed in section 1.2.2.1, the subtypes are known to differ in the presentation of symptoms, executive function, and co-morbidity profiles. Whether sleep differs between ADHD subtypes, however, is not well understood, and only three studies have investigated subtype differences in the sleep of children with ADHD. One study reported no differences in the profile of sleep disorders or behaviours among children with ADHD-I, ADHD-H/I, and ADHD-C (Wiggs et al., 2005). Two studies, however, reported differences between ADHD subtypes (LeBourgeois et al., 2004; Mayes et al., 2009). LeBourgeois et al. (2004) found that children with ADHD, particularly the ADHD-I group, had more daytime sleepiness than healthy controls. Mayes et al. (2009) also found that ADHD-I had more daytime sleepiness and longer sleep, while ADHD-C had more sleep problems such as trouble falling asleep, restlessness and waking during sleep, and nightmares. Finally, in a study that was not designed to compare ADHD subtypes, Kirov et al. (2007) compared healthy and ADHD children with or without tic disorders, and with a multiple regression analysis revealed that inattention correlates with short sleep onset latency, while hyperactivity correlates with decreased REM sleep percentage and increased sleep stage cycling.

Differences in the presentation of symptoms and co-morbidities in ADHD subtypes have been reported to stem from differences in neurological mechanisms underlying ADHD-I and ADHD-C. The observation that the ADHD-I subtype is associated with under-arousal, and the ADHD-C subtype is associated with higher levels of energy is interesting in the context of sleep disorders, because arousal levels may directly relate to sleep disorders (Laufer et al., 1957; Satterfield et al., 1974; Fisher and Rinehart, 1990; Ball et al., 1997). In this regard, a problem of under-arousal in ADHD-I may be associated with excessive daytime sleepiness and hypersomnia, whereas a problem of over-arousal in ADHD-C may be associated with difficulty initiating/maintaining sleep, and RLS (Mayes et al., 2009). Thus, while both ADHD-I and ADHD-C
subtypes are associated with sleep problems, the two subtypes may be associated with different sleep pathologies.

While there is some evidence in the childhood ADHD population that the profile of sleep disorders differs in ADHD subtypes, whether adult ADHD subtypes differ in the presentation of sleep disorders is currently unknown, and has not hitherto been studied. Therefore, the general aim of this study was to investigate whether there are differences in sleep disorder profiles between adult ADHD subtypes. To this end, I collected subjective and objective correlates of sleep from adults diagnosed with ADHD-I and ADHD-C as described in the Materials and Methods section, and I formulated the following hypotheses:

**Main Hypothesis:** There are significant differences in the nature and prevalence of sleep disturbances afflicting adults with ADHD-I and adults with ADHD-C.

**Hypothesis 1:** Subjective correlates of sleep such as daytime sleepiness, fatigue, and sleep quality differ in adults diagnosed with ADHD-I and adults diagnosed with ADHD-C.

**Hypothesis 2:** The circadian regulation of sleep-wake cycles in ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality differs in ADHD-I and ADHD-C groups.

In this regard:

**Hypothesis 2a:** Correlates of circadian phase such as subjective circadian preference and melatonin secretion profiles differ in ADHD-I and ADHD-C groups.

**Hypothesis 2b:** Associations between correlates of circadian phase and the core symptoms of ADHD differ in ADHD-I and ADHD-C groups.

**Hypothesis 3:** Objective measures of sleep in ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality differ in ADHD-I and ADHD-C groups.

In this regard:
**Hypothesis 3a:** The macrostructure of sleep differs in ADHD-I and ADHD-C groups.

**Hypothesis 3b:** The prevalence of sleep-disordered breathing differs in ADHD-I and ADHD-C groups.

**Hypothesis 3c:** The prevalence of periodic limb movements in sleep differs in ADHD-I and ADHD-C groups.

**Hypothesis 3d:** Associations between objective measures of sleep and the core symptoms of ADHD differ in ADHD-I and ADHD-C groups.
Chapter 2
MATERIALS AND METHODS

2.1 Study design

This was an observational study of patients diagnosed with ADHD-I or ADHD-C. The study was divided into two phases: subjective data were collected during Phase I of the study to diagnose and characterize ADHD subtypes, and to address Hypothesis 1; and objective data were collected during Phase II of the study to address Hypotheses 2 and 3.

2.2 ADHD diagnostic tools

There are currently no physical or genetic markers, blood tests, or imaging studies that can unequivocally identify ADHD (Furman, 2005), and although there is some emerging evidence that suggests that EEG-based methodologies may aid in differentiating ADHD from non-ADHD subjects (reviewed by Loo & Makeig, 2012), the diagnosis of ADHD is currently based on clinical observation of the symptoms that impair the individual.

In addition to the DSM-IV-TR ADHD symptoms checklist, there are a number of rating scales and questionnaires that have been developed over the years to aid in the screening and diagnosis of adult ADHD. These include the Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2006), the Weiss Functional Impairment Rating Scale (WFIRS) (Weiss, 2010), the Wender Utah ADHD Rating Scale (WURS) (Ward et al., 1993), and the Conners’ Adult ADHD Rating Scale (CAARS) (Conners et al., 1999). More recently, the Temperament and Character Inventory (TCI) has also been used in some research and clinical settings as a tool to diagnose ADHD, given the TCI’s unique ability to provide information on personality and character trait combinations that are characteristic of ADHD (Pennington & Ozonoff, 1996; Downey et al., 1996; 1997; Anckarsater et al., 2006; Jacob et al., 2007; Cho et al., 2009; Faraone et al., 2009). Of these tools, ASRS, CAARS, and TCI were used in this study for diagnosis of ADHD.
2.2.1 ASRS

The ASRS is an 18-item rating scale derived from the DSM-IV-TR criteria under the guidance of the World Health Organization (Kessler et al., 2006). The scale is divided into sections A and B, and each section has shaded areas that reflect significant symptoms which are rated on a frequency basis: “Never”, “Rarely”, “Sometimes”, “Often”, and “Very Often”. Part A consists of six questions of which four are required for diagnosis of ADHD, and part B consists of 12 questions that have not shown to add any strength to the screening mechanism.

The ASRS has been translated into 50 languages, and it has been validated using the National Co-morbidity Survey cohort and a representative sample from health plan members: test-retest reliability is 0.58-0.77, internal consistency reliability of the continuous ASRS screener is 0.63-0.72, and there is substantial agreement for individual items and significant kappa coefficients for all items (p<0.001) (Biederman et al., 1993; Schweitzer et al., 2001). Moreover, it has a sensitivity of 84% and a specificity of 66% (van de Gling et al., 2013).

2.2.2 CAARS

The CAARS – self-report: long version (CAARS-S:L) is an 84-item self-report questionnaire used to assess the current symptoms of ADHD (Conners et al., 1999). The threshold is 62 with items being scored as 0 for “none of the time”, 1 for “some of the time”, 2 for “most of the time”, and 3 for “all of the time”. CAARS covers all of the adult ADHD symptoms and it allows for the diagnosis of the Hyperactive-Impulsive, Inattentive, or Combined ADHD subtypes based on scores on 8 subscales that address Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, Problems with Self-Concept, DSM-IV Inattentive Symptoms, DSM-IV Hyperactive-Impulsive Symptoms, DSM-IV ADHD Symptoms Total, and ADHD Index.

In terms of psychometrics, CAARS has a sensitivity of 71%, a specificity of 75%, and an overall diagnostic efficiency rate of 85% (Conners et al., 1999). Moreover, its test-retest reliability is 0.89, its rater-interrater agreement is 0.67, and Cohen’s alpha for internal consistency ranges between 0.86 and 0.92 (Epstein & Kollins, 2006).
2.2.3 TCI

The TCI is a 240-item inventory that uses a True or False answering system with the patient’s responses entered into a computer scoring system. The system produces a report in a multidimensional psychobiological model that explains personality as a product of any factorial combination of its four dimensions of temperament (Novelty Seeking, Harm Avoidance, Reward Dependence, and Persistence) and three dimensions of character (Self-Directedness, Cooperativeness, and Self-Transcendence) (Cloninger et al., 1993; Svrakic et al., 1993; Kose, 2003).

In terms of psychometrics, the internal consistency of the TCI (Cohen’s alpha) is 0.76-0.87 for temperament, and 0.84-0.89 for character (Cloninger et al., 1993). Moreover, it has been reported that the TCI test-retest reliability is 0.52-0.72 for temperament, and 0.52-0.71 for character in Korean college students (Sung et al., 2002).

2.3 Assessment of sleep and its related variables

2.3.1 Subjective measures of sleep

Subjective data on sleepiness, sleep quality, circadian phase, and fatigue were collected using the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ), and Fatigue Severity Scale (FSS), respectively.

2.3.1.1 Epworth Sleepiness Scale

ESS is a self-administered scale that evaluates a subject’s general level of sleepiness by asking respondents to rate their “likelihood to doze or fall asleep” in eight different situations (Johns, 1991). The global ESS score – which ranges from 0 to 24 – serves as a subjective measure of daytime sleepiness: higher scores indicate more sleepiness, and a score of 10 or higher indicates pathological sleepiness (Johns, 1991; Shahid et al., 2010).
In terms of psychometrics, it has been reported that ESS has diagnostic sensitivities of 63% and 93.5% in OSA and Narcolepsy patients, respectively (Johns et al., 2000; Rosenthal & Dolan, 2008). Moreover, the correlation coefficient for test-retest reliability of ESS is 0.822, and Cronbach’s alpha for internal consistency is 0.88 (Johns, 1992; 1994; 2000; Rosenthal et al., 1993).

### 2.3.1.2 Pittsburgh Sleep Quality Index

PSQI is a self-rated, 9-item questionnaire that assesses quality of sleep over the past month. The global PSQI score – which ranges from 0 to 21 – serves as a subjective measure of sleep quality: higher scores indicate worse sleep quality, and a score of 5 or higher indicates poor sleep quality (Buysse et al., 1989).

PSQI has been validated in different medical populations (Carpenter & Andrykowski, 1997; Seidel et al., 2009), and in different ethnicities (Doi et al., 2000; Shochat et al., 2007; Farrahi et al., 2008). In terms of psychometrics, PSQI has a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa=0.75, p<0.001) in distinguishing good sleepers from poor sleepers (Buysse et al., 1989), an internal consistency (Cohen’s alpha) of 0.87, and a rater-interrater agreement (kappa coefficient) of 0.75 (Backhaus et al., 2002).

### 2.3.1.3 Horne-Ostberg Morningness-Eveningness Questionnaire

MEQ is a self-administered questionnaire that assesses circadian function by the use of questions regarding timing for activities and sleep-wake cycles. MEQ scores correlate with temperature fluctuations, which are well known to follow a circadian rhythm that influences sleep-wake cycles, as well as levels of alertness (Horne & Ostberg, 1976; Coleshaw et al., 1983; Van Someren et al., 2002). MEQ scores are used to identify chronotypes: MEQ scores of 6-10 indicate a definite evening type, scores of 11-15 indicate a moderate evening type, scores of 16-22 indicate an intermediate type, scores of 23-27 indicate a moderate morning type, and scores of 28-32 indicate a definite evening type. While data on psychometrics is scarce, MEQ has been reported to have an internal consistency of 0.87 (Backhaus et al., 2002).
2.3.1.4 Fatigue Severity Scale

FSS is a self-administered 9-item scale that determines a subject’s trait fatigue. The global FSS score – which ranges from 1 to 9 – serves as a subjective measure of fatigue, with higher scores indicating more fatigue (Krupp et al., 1989).

In terms of psychometrics, FSS has been reported to have a test-retest reliability of 0.84, an internal consistency (Cronbach’s alpha) of 0.88, and rater-interrater agreement of 0.75 (Mattsson et al., 2008; Shahid et al., 2010). Moreover, FSS has been reported to distinguish fatigue in healthy controls and patients with systemic lupus erythematosus or multiple sclerosis (Krupp et al., 1989), and in different medical populations (Lichstein et al., 1997; Kleinman et al., 2000; Herlofson & Larsen, 2002; Mattsson et al., 2008).

2.3.2 Objective measures of sleep

Objective data on sleep and circadian phase were collected by means of 2 nights of PSG recordings and a dim light melatonin onset (DLMO) test, respectively.

2.3.2.1 Polysomnography

PSG is a technique by which physiological parameters, including brain surface activity, heart activity, muscle activity in the limbs and chin, eye movements, and respiratory correlates are monitored during sleep. It is a tool for objectively documenting and quantitating abnormal physiological manifestations during sleep (Bloch, 1997).

PSG recordings were collected over two separate nights with a lapse of no more than a week between recordings. On the first night of PSG, subjects retired to bed at a fixed time of 2300 h and were awoken the next morning at a fixed time of 0700 h, thus creating an imposed sleep period. On the second night of PSG, subjects were left to choose bedtime and waking time.

A standard montage including EEG, EOG, EMG, and respiratory monitoring (oxygen saturation, nasal airflow, and breathing effort) was used. The sleep parameters included total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL), REM sleep latency (REML),
REM periods, awakenings, stage representation (stage 1, stage 2, SWS, and REM sleep percentages), periodic limb movements per hour of sleep (PLMI), apneas/hypopneas per hour of sleep (AHI), arousals associated with periodic limb movement per hour of sleep (PLMA), arousals associated with apneas/hypopneas per hour of sleep (AHA), respiratory event related arousals per hour of sleep (RERA), and spontaneous arousal per hour of sleep (SAI).

First, all EEG sites of the scalp were marked with a red wax pen for easy localization. After this, all EEG, EOG, EMG, and ECG sites were cleaned with alcohol, and then a small amount of skin prep gel was placed on the designated electrode sites. Following this, a small amount of conductive paste was added directly onto the electrode cups, which were then placed on the designated sites and secured in place with either gauze (for electrode sites on the scalp) or surgical tape (all other electrode sites).

Electrodes were placed bilaterally – that is, on the right side and on the left side of the body – on the outer canthus of the eye (one slightly above, the other slightly below the horizontal axis of the eyes) for EOG; on the mentalis/submentalis muscles of the chin for EMG (for detection of muscle atonia during REM sleep); on the anterior tibialis for EMG (for assessment of limb movements); and on the chest, just below the collarbone, for ECG. Following the International 10-20 System, EEG electrodes were placed on the midline of the scalp (reference electrode Cz) and the forehead (ground electrode), and bilaterally behind the ears (electrodes A1 and A2), on the sides of Cz (C3 and C4), on the frontal lobes (F3 and F4), and on the occipital lobes (O1 and O2). Ancillary channels were used to document respiratory effort (by thoracoabdominal excursions, respiratory inductive plethysmography), oronasal airflow (by nasal airflow pressure transducer), and oxygen saturation (by pulse oxymetry).

PSG recordings were scored by a single-blinded scorer according to standardized criteria (Rechtschaffen & Kales, 1968). SOL was defined as the first 30 s epoch of stage 2 sleep. AHI scoring was based on nasal pressure monitoring, and apnea/hypopneas were scored according to American Academy of Sleep Medicine Task Force rules (AASM Task Force, 1997). Arousals were scored according to Sleep Disorders Atlas Task Force rules (Bonnet et al., 2007).
2.3.2.2  Dim light melatonin onset test

Melatonin is a reliable marker of SCN function and it is secreted in the dark (Shanahan et al., 1997; Van der Heijden et al., 2005; Pandi-Perumal et al., 2007). The rise in melatonin typically precedes sleep by an average of 1-3 h (Burgess et al., 2002). Subjects underwent DLMO test to establish circadian phase.

Sample collection for melatonin was conducted as previously described (Rahman et al., 2009). Briefly, study subjects were asked to report to the sleep clinic at least 30 minutes prior to the first saliva collection, such that the first sample would represent melatonin secretion after having been in the dark (luminescence < 30 lux) for 30 minutes. Study subjects remained in the dark from 1830 to 0200 h and saliva samples were acquired hourly from 1900 to 0200 h. Saliva specimens were collected using the Sali-Saver™ (American Laboratory Products Company, NH, USA), and were stored at -20°C until the samples were sent to a University Health Network laboratory for analysis. Salivary melatonin was assessed with a Direct Saliva Melatonin enzyme-linked immunoabsorbent assay (ELISA) kit from Buhlman Laboratories (Allschwill, Switzerland). All saliva specimens from a given subject were analyzed with the same assay kit with an assay functional sensitivity of 1.3 pg/ml. DLMO, defined as the point at which melatonin secretion begins, was used as a marker of the circadian phase. DLMO was set as the time of the sampling of the first salivary sample that reached a minimum value of 4pg/ml that remained elevated in the subsequent sampling times (Nagtegaal et al., 1998; Martin & Eastman, 2000).

2.4  Recruitment Process

2.4.1  Phase I

The participants of this study were subjects referred to the Centre for Addiction and Mental Health (CAMH) between June 2009 and June 2010 for an assessment of ADHD. Referred subjects were contacted consecutively to complete the ASRS, the CAARS-S:L, the DSM-IV-TR Checklist of Symptoms, and the TCI; as well as the subjective measures of sleep listed in Section 2.3.1.
Subjects with T-scores > 72 on CAARS subscales corresponding to DSM-IV ADHD symptoms, and/or at least 4/6 positive items on the ASRS, and/or at least 6/9 positive items on the DSM-IV-TR Checklist for Inattentive Symptoms, and/or a TCI score < 30th percentile on the self-directedness subscale were considered to meet criteria for ADHD and, thus, were booked appointments for a board-certified psychiatrist-led semi-structured interview, which served to assess presenting symptoms and clinical history, and thus confirm/reject ADHD diagnosis. Clinical history in childhood was confirmed by interviewing a collateral (one of the patient’s parents, older siblings, or spouse (if they knew the patient’s history)). A Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used to rule out any concurrent psychopathologies.

2.4.1.1 Inclusion criteria

i. Subjects between the ages of eighteen and sixty-five

ii. An ADHD diagnosis based on criteria listed in Section 2.4.1

iii. English proficiency

iv. Clinical history in childhood confirmed by collateral as stated in Section 2.4.1

v. Signed consent form 173/2009 (see appendix V)

2.4.1.2 Exclusion criteria

i. Subjects on psychotropic medications within the last month

ii. Subjects with a concurrent Axis I disorder other than ADHD

iii. Night shift workers
2.4.1.3 Determination of ADHD subtypes

ADHD subtype for each subject was determined using the following information:

i. Information on severity of Hyperactivity-Impulsivity symptoms obtained from the DSM IV-TR ADHD Symptoms Checklist.

ii. Information on severity of Hyperactivity-Impulsivity symptoms obtained from CAARS subscales corresponding to Hyperactivity/Restlessness and Impulsivity/Emotional Lability.

iii. Information on current presentation of Inattention and/or Hyperactivity-Impulsivity symptom dimensions obtained from a semi-structured clinical interview with the subject.

iv. Information on clinical history – specifically, whether the subject displayed externalizing behaviour and/or symptoms of Hyperactivity-Impulsivity during childhood – obtained from an interview with the subject’s collateral.

The information obtained from these four sources was integrated using the flowchart shown in Figure 2.1 to determine ADHD subtype classification.
2.4.1.4 Subject demographics

As shown in figure 2.2, a total of 284 adults were referred to CAMH during this study, and 158 subjects were excluded on account of being on psychotropic medication(s) (n = 5), not being between the ages of 18-65 (n = 15), not meeting criteria for ADHD (n = 41), the presence of co-morbid Axis-I disorder(s) (n = 47), and not providing consent to participate in this phase of the study (n = 50).
A total of 126 subjects accepted the invitation to participate in Phase I of the study and each gave informed consent in writing. The Research Ethics Board at CAMH approved the procedures for the protocol and the investigation was conducted according to the principles expressed in the Declaration of Helsinki and the Belmont report.

Figure 2.2 Schematic representation of patient enrollment into Phase I of the study
2.4.2  Phase II

On the assumption that subjects with sleep disturbances and/or sleep disorders would have
complaints of excessive daytime sleepiness and/or poor sleep quality, subjects with $\text{ESS} \geq 8$ and
$\text{PSQI} \geq 5$ were identified and invited to participate in the second phase of the study for the
objective assessment of sleep by means of two PSG recordings and one DLMO test collected
over the course of three separate nights.

2.4.2.1  Inclusion criteria

i.  Criteria i-v of section 2.4.1.1

ii.  $\text{ESS} \geq 8$ and/or $\text{PSQI} \geq 5$

iii.  Signed consent form 128/2009 (see appendix VI)

2.4.2.2  Exclusion criteria

i.  Criteria listed in Section 2.4.1.2

2.4.2.3  Subject demographics

A total of 79 subjects initially accepted the invitation to participate in Phase II of the study and
each gave informed consent in writing. The Research Ethics Board at CAMH approved the
procedures for the protocol and the investigation was conducted according to the principles
expressed in the Declaration of Helsinki and the Belmont report.

Of the 79 subjects initially signed up for this phase of the study, 11 subjects dropped out prior to
the study, and 7 subjects dropped out after the first night of PSG citing time constraints as
reasons for dropping out. Thus, 61 subjects completed the study and for 7 subjects, PSG data
were collected for only one night. Moreover, 5 subjects who completed the study yielded
insufficient/uninterpretable data on the DLMO tests and, thus, the final sample for the DLMO
tests was 56.
2.5 Sample Size

Two sample sizes were calculated for this study: the sample size needed for analysis of Phase I data (questionnaires); and the sample size needed for analysis of Phase II data (PSG and DLMO).

First, sample size needed for Phase II data was determined using the computer software G*Power 3, which calculates sample sizes based on the principles of Cohen (i.e. effect size, power, p-value, sample size, and standard deviation are interrelated, and one item can be calculated if all other 4 items are known). For mixed between-within subjects multiple analysis of variance with 2 groups (ADHD-I and ADHD-C) and two measurements (PSG night 1 and PSG night 2), with 80% power, medium-large effect size ($f=0.35$) and significance level set at $p=0.05$, the minimum sample size required is 67.

Then, for Phase I, sample size was determined based on the formula determined by Tabachnik & Fidell (2001), according to which the number of subjects should be 5 to 20 times the number of variables in a model of multivariate analysis for stable reliability and validity estimates. There were a total of 4 dependent variables (PSQI, ESS, FSS, MEQ) and 1 independent variable stratified into two groups (ADHD-I and ADHD-C). Therefore, there were 8 cells. Since $8\times5=40$ and $8\times20=160$, the total sample size required to detect significant differences between groups for multiple comparisons was between 40 and 160.

Determination of the sample size for Phase I was done taking into consideration the sample size required for Phase II, because patients for Phase II needed to be recruited from the patient pool of Phase I. Since 67 patients were needed from the Phase I pool, and assuming that sleep disorders occur at a rate of 50% in adult ADHD, the sample size required for Phase I was calculated to be 134, which fell between the required values of 40 and 160. Thus, the following sample sizes were determined to be required for the study:

- For Phase I: Between 80 to 160 subjects, preferably around 134 subjects.
- For Phase II: 67 subjects.

The final sample size for Phase I was $n = 126$, and the final sample size for Phase II was $n = 68$. 
2.6 Ethics

All participants were advised according to a standard Regulated Health Practitioners Act based informed consent form filled out by the caregiver. Participants were advised that they may drop out of the study at any time without penalty. There was no remuneration for participation.

2.7 Statistics

Statistical analyses were carried out with SPSS for Mac OS (Version 19) software package. Outlier analyses were conducted, whereby implausibly high or low values were removed.

2.7.1 Phase I

2.7.1.1 Symptomatology and personality profiles in ADHD subtypes

Statistical significance for all tests was set at $p = 0.01$ to compensate for the use of multiple statistical tests. A student’s t-test was used to compare mean age in ADHD-I and ADHD-C groups. Chi-squared test was used to determine gender distribution in ADHD subtypes. Inspection of the data plots, skew, and kurtosis revealed that the percentile ranks of the TCI dimensions of Novelty Seeking, Harm Avoidance, and Self-Directedness; and the T-scores of the CAARS subscale corresponding to Problems with Self-Concept were not normally distributed. Thus, Mann-Whitney U tests were used to compare CAARS, ASRS, DSM-IV-TR, and TCI scores in ADHD subtypes.

2.7.1.2 Subjective measures of sleep and daytime function in ADHD subtypes

Statistical significance for all tests was set at $p = 0.01$ to compensate for the use of multiple statistical tests. Mann-Whitney U test was used to compare sleep quality ratings (measured using PSQI) in ADHD subtypes. Chi-squared test was used to determine distribution of subjects with 1-3, 4-6, or 7-10 sleep problems in ADHD subtype groups. Multivariate analysis of covariance (MANCOVA) controlling for the effects of age and gender was conducted to compare Bedtime, Rise Time, Total Sleep Time (TST), and Sleep Onset Latency (SOL) (measured using
PSQI) in ADHD subtype groups. 2-way MANCOVA controlling for the effect of age was conducted to compare ESS, PSQI, and FSS scores in ADHD subtype groups and in gender groups. Partial Pearson correlations controlling for the effects of age and gender were conducted to examine underlying relationships between sleep-related variables (i.e. ESS, PSQI, and FSS) in ADHD-I and ADHD-C groups. Two-tailed Pearson correlation coefficient critical values for \( p = 0.01 \) and \( n = 45 \) (for ADHD-I) or \( n = 80 \) (for ADHD-C) were calculated using Microsoft Excel.

### 2.7.2 Phase II

Preliminary assumption testing was conducted to check for normality, linearity, univariate and multivariate outliers, homogeneity of variance-covariance matrices, and multicollinearity, with no serious violations except where noted. Pillai’s trace was used in place of Wilk’s \( \lambda \) for MANCOVAs to compensate for any violations of assumptions, and if the assumption of equality of error variances was violated, significance for tests of between-subjects effects was set at \( p = 0.01 \) as recommended by Tabachnick & Fidell (2001). Moreover, where dependent variable values were not normally distributed, parametric tests were conducted on the ranked values rather than the absolute values as recommended by Connover & Iman (1981).

#### 2.7.2.1 Circadian phase in ADHD subtypes

Chi-square tests were conducted to examine subject frequency distributions according to ADHD subtype (i.e. ADHD-I and ADHD-C), chronotype (i.e. morning chronotype, intermediate chronotype, and evening chronotype), gender, and timing of DLMO (i.e. subjects with delayed DLMO and subjects with normal DLMO). Analysis of variance (ANOVA) was conducted to compare mean age in ADHD subtype groups. A separate ANOVA, using Bonferroni post-hoc tests, was conducted to compare age in chronotype groups. Analysis of co-variance (ANCOVA) controlling for the effects of age and gender was conducted to compare MEQ scores in ADHD subtype groups. 2-way ANCOVA controlling for the effects of gender and ranked age was conducted to examine the effects of ADHD subtype and chronotype on ranked values of DLMO. Bonferroni post-hoc tests were conducted to examine differences in chronotype groups.
Pearson partial correlations between the ranked values of DLMO, MEQ scores, and DSM-IV-I and DSM-IV-H/I T-scores while controlling for the effects of gender and ranked age were conducted to examine relationships between DLMO, MEQ and the core symptoms of ADHD in ADHD subtype groups. Because five partial correlations were conducted per ADHD subtype group, the p-value was adjusted to 0.01. Two-tailed Pearson correlation coefficient critical values for $p = 0.01$ and $n = 23$ (for ADHD-I) or $n = 33$ (for ADHD-C) were calculated using Microsoft Excel.

### 2.7.2.2 Objective assessment of sleep in ADHD subtypes

Examination of data revealed that some of the collected PSG variables were not normally distributed and, thus, all statistical analyses were conducted on ranked values as recommended by Connover & Iman (1981). Except where noted, all statistical tests were conducted to compare ADHD subtype groups while controlling for gender, ranked age and the ranked values of DLMO. ANCOVA controlling for DLMO time was conducted to compare mean age. Chi-squared test was conducted to determine gender distribution in ADHD subtypes. Chi-square tests were conducted to determine the distribution of subjects according to severity of PLMS and SDB based on PLMI and AHI values obtained on the first night of PSG. Repeated-measures MANCOVA was conducted to compare PSG parameters of sleep architecture (i.e. AHI, PLMI, AHA, PLMA, RERA, SAI, TST, SE, SOL, REML, awakenings, REM periods, and percentages of stage 1, stage 2, SWS, and REM sleep). Pearson partial correlations were conducted to examine underlying relationships between variables of PSG and CAARS subscales corresponding to Inattention/Memory Problems, Hyperactivity/Restlessness, and Impulsivity/Emotional Lability. Because 14 partial correlations were conducted per ADHD subtype group, the p-value was adjusted to 0.002. Two-tailed Pearson correlation coefficient critical values for $p = 0.002$ and $n = 27$ (for ADHD-I) or $n = 41$ (for ADHD-C) were calculated using Microsoft Excel.
Chapter 3
RESULTS

3.1 Phase I

In this phase of the study, subjective data on ADHD symptoms severity, personality traits, and sleep problems were collected from ADHD-I and ADHD-C subjects referred to the Centre for Addiction and Mental Health to characterize study subjects, and to test Hypothesis 1: Subjective correlates of sleep such as daytime sleepiness, fatigue, and sleep quality differ in adults diagnosed with ADHD-I and adults diagnosed with ADHD-C.

3.1.1 Characterization of study subjects

Data were collected from 126 ADHD subjects, of whom 45 were diagnosed with ADHD-I (19-60 years of age, mean 40 ± 11 years, 24% females) and 81 were diagnosed with ADHD-C (20-62 years of age, mean 37 ± 10 years, 27% females). The two groups did not differ with regards to mean age \([t_{126} = 1.49; p = 0.14]\) or gender distribution \([\chi^2_{1,126} = 0.11; p = 0.74]\).

Subject scores on ASRS, DSM-IV Symptoms Checklist, and CAARS subscales corresponding to Inattention/Memory Problems, Hyperactivity/Restlessness, Impulsivity/Emotional Lability, and Problems with Self-Concept were examined to compare core symptoms severity in ADHD subtypes. As indicated in Table 3.1, the subjects of this study on average scored highly on measures of Inattention and Memory Problems by both CAARS and DSM-IV Symptoms Checklist; and above average on the CAARS subscales of Impulsivity/Emotional Lability and Problems with Self-Concept. Mann-Whitney tests indicate that while the score distributions of these subscales were comparable between ADHD subtypes, measures of hyperactivity were significantly higher \((p \leq 0.01)\) for ADHD-C subjects by both CAARS \([U = 682.0, Z = -4.38]\) and the DSM-IV Symptoms Checklist \([U = 743.5, Z = 3.99]\) (Table 3.1).

Personality traits were examined in study subjects using the TCI. An examination of TCI score distributions indicated that, as a whole, study subjects were average on the dimensions of
Reward Dependence and Cooperativeness, low on Persistence, and very low on Self-Directedness regardless of ADHD subtype. On the other hand, ADHD-I subjects scored significantly lower on the dimensions of Novelty Seeking and Self-Transcendence, and significantly higher on Harm Avoidance than ADHD-C subjects (Table 3.1).

### Table 3.1 ADHD rating scale scores in ADHD-I and ADHD-C subjects

<table>
<thead>
<tr>
<th></th>
<th>ADHD-I (n = 45)</th>
<th>ADHD-C (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>ASRS (number of items)</td>
<td>5</td>
<td>47.40</td>
</tr>
<tr>
<td>DSM-IV Inattentive Symptoms</td>
<td>7</td>
<td>52.61</td>
</tr>
<tr>
<td>DSM-IV Hyperactive/Impulsive Symptoms</td>
<td>4</td>
<td>37.43</td>
</tr>
<tr>
<td>CAARS (T-scores)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention/Memory Problems</td>
<td>77</td>
<td>55.18</td>
</tr>
<tr>
<td>Hyperactivity/Restlessness</td>
<td>56</td>
<td>39.09</td>
</tr>
<tr>
<td>Impulsivity/Emotional Lability</td>
<td>63</td>
<td>48.99</td>
</tr>
<tr>
<td>Problems with Self-Concept</td>
<td>70</td>
<td>64.39</td>
</tr>
<tr>
<td>TCI (percentiles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novelty Seeking Behaviour</td>
<td>70</td>
<td>43.99</td>
</tr>
<tr>
<td>Harm Avoidance</td>
<td>93</td>
<td>78.40</td>
</tr>
<tr>
<td>Reward Dependence</td>
<td>45</td>
<td>53.18</td>
</tr>
<tr>
<td>Persistence</td>
<td>35</td>
<td>66.54</td>
</tr>
<tr>
<td>Self-Directedness</td>
<td>5</td>
<td>60.29</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>45</td>
<td>58.67</td>
</tr>
<tr>
<td>Self-Transcendence</td>
<td>10</td>
<td>49.84</td>
</tr>
</tbody>
</table>

Abbreviations: ASRS – Adult ADHD Self-Report Scale; CAARS – Conner’s Adult ADHD Rating Scale; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; TCI – Temperament and Character Inventory.

Mann-Whitney U tests conducted to compare ADHD-I (n = 45) and ADHD-C (n = 81) subtype groups revealed statistically significant differences with respect to the CAARS subscale corresponding to Hyperactivity/Restlessness; DSM-IV symptoms of Hyperactivity/Impulsivity; and TCI scales corresponding to Novelty Seeking Behaviour, Harm Avoidance, and Self-Transcendence.

*a U = 743.5, Z = 3.99, p ≤ 0.01
*b U = 682.0, Z = -4.38, p ≤ 0.01
*c U = 942.5 , Z = -3.84, p ≤ 0.01
*d U = 926.5, Z = -3.91, p ≤ 0.01
*e U = 1182.5, Z = -2.51, p ≤ 0.01
3.1.2 Correlates of sleep

3.1.2.1 Subjective measures of sleep and sleep quality

PSQI was used to collect data pertaining to sleep quality: ADHD patients go to bed at around 12:30AM, wake up at around 8:15AM, and with an SOL that averages at around 27 minutes, patients sleep a little over 6 ½ hours (Table 3.2). While there were no significant subtype differences on any of these sleep parameters \([F_{4,101} = 0.992, p = 0.42]\), the perception of sleep – which was measured with PSQI – appears to differ between subtypes: when subjects were asked to rate their sleep (0 = very good, 1 = fairly good, 2 = fairly bad, 3 = very bad), median latencies for sleep ratings in ADHD-I and ADHD-C groups were 2 and 1 (mean ranks 67.12 and 52.07, respectively), and the distributions in the two groups differed significantly \((U = 1031.5, Z = -2.53, p = 0.01)\), indicating poorer sleep quality ratings in ADHD-I patients.

In order to determine whether ADHD subtypes differ with respect to the types of sleep problems subjects are affected by, I examined responses to item 5 of the PSQI, which addresses a number of sleep problems as listed in Table 3.3. The four most common sleep problems in ADHD patients, regardless of subtype, were initial insomnia, interrupted sleep, getting up to use the bathroom, and feeling too hot.

Several subjects reported more than one sleep problem. To determine whether any one of the subtypes is associated with a higher number of sleep problems, I stratified the data into groups of patients who experienced 1-3, 4-6, or 7-10 of the sleep problems addressed by item 5 of the PSQI. As indicated in Table 3.4, approximately 40% of ADHD patients reported 4-6 sleep problems and, while the ADHD-C group had a higher percentage of patients reporting 7-10 sleep problems than the ADHD-I group, a chi-squared test revealed no significant differences between ADHD-I and ADHD-C patient groups \(\chi^2_{2, 11} = 1.79, p = 0.41\).
Table 3.2 Subjective measures of sleep

<table>
<thead>
<tr>
<th></th>
<th>ADHD-I (n = 45)</th>
<th>ADHD-C (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleep onset latency (min)</strong></td>
<td>27 (±21)</td>
<td>29 (±25)</td>
</tr>
<tr>
<td><strong>Total sleep time (h)</strong></td>
<td>6.81 (±1.22)</td>
<td>6.82 (±1.38)</td>
</tr>
<tr>
<td><strong>Bedtime</strong></td>
<td>12:21 AM (±119’)</td>
<td>12:38 AM (±107’)</td>
</tr>
<tr>
<td><strong>Rise time</strong></td>
<td>8:17 AM (±141’)</td>
<td>8:09 AM (±130’)</td>
</tr>
<tr>
<td><strong>Sleep Rating (median and mean rank)</strong></td>
<td>2 (67.12)</td>
<td>1 (52.07)</td>
</tr>
</tbody>
</table>

Information on Sleep Onset Latency, Total Sleep Time, Bedtime, and Rise Time were obtained using the Pittsburgh Sleep Quality Index. No statistical differences were found between ADHD subtypes.

* F<sub>4,101</sub> = 0.992, p = 0.416 (IV = subtype, CV = age and gender)
* U = 1031.5, Z = -2.53, p = 0.01
* 0 = very good, 1 = fairly good, 2 = fairly bad, 3 = very bad

Table 3.3 Types and frequency of sleep problems in ADHD subtypes

<table>
<thead>
<tr>
<th>Type of Sleep Problem</th>
<th>ADHD-I (n = 45)</th>
<th>ADHD-C (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot get to sleep within 30 minutes*</td>
<td>29 (64%)</td>
<td>59 (72%)</td>
</tr>
<tr>
<td>Wakes up in the middle of the night or early morning*</td>
<td>29 (64%)</td>
<td>62 (76%)</td>
</tr>
<tr>
<td>Needs to use bathroom*</td>
<td>26 (57%)</td>
<td>60 (74%)</td>
</tr>
<tr>
<td>Cannot breath comfortably</td>
<td>8 (17%)</td>
<td>20 (24%)</td>
</tr>
<tr>
<td>Coughs or snores loudly</td>
<td>14 (31%)</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>Feels too cold</td>
<td>16 (35%)</td>
<td>35 (43%)</td>
</tr>
<tr>
<td>Feels too hot*</td>
<td>21 (46%)</td>
<td>45 (55%)</td>
</tr>
<tr>
<td>Has bad dreams</td>
<td>16 (35%)</td>
<td>37 (45%)</td>
</tr>
<tr>
<td>Has pain</td>
<td>9 (20%)</td>
<td>35 (43%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (26%)</td>
<td>29 (35%)</td>
</tr>
</tbody>
</table>

Information on types and frequency of sleep problems afflicting subjects was obtained using the Pittsburgh Sleep Quality Index. χ² tests conducted to determine the proportions of subjects with each of the listed sleep problems in ADHD-I and ADHD-C groups revealed no statistical significance.
*Most commonly reported sleep problems

Table 3.4 Distribution of ADHD subjects according to number of sleep problems

<table>
<thead>
<tr>
<th>Number of sleep problems</th>
<th>ADHD-I (n = 45)</th>
<th>ADHD-C (n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>11 (29.7%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>4-6</td>
<td>16 (43.2%)</td>
<td>32 (42.6%)</td>
</tr>
<tr>
<td>7-10</td>
<td>10 (27%)</td>
<td>28 (37.3%)</td>
</tr>
</tbody>
</table>

Data were reorganized to assess proportions of subjects with 1-3, 4-6, and 7-10 sleep problems. χ² tests conducted to determine the distribution of subjects according to number of sleep problems in ADHD-I and ADHD-C groups revealed no statistical significance (χ²<sub>2,112</sub> = 1.79, p = 0.41).
3.1.2.2 Subjective measures of sleepiness and fatigue

In ADHD, the study of sleep is particularly important because it pertains to daytime function, which is already compromised in patients with ADHD. In addition to data on sleep quality, data on sleepiness and fatigue were collected by means of ESS and FSS, respectively. MANCOVA was conducted to evaluate the effects of ADHD subtype and gender on daytime sleepiness, sleep quality, and fatigue indicated statistical significance \(F_{3,119} = 4.47; p = 0.005; \text{partial } \varepsilon^2 = 0.1; \text{power to detect the effect} = 0.87; \text{Wilk’s lambda} = 0.90\]. Tests of between-subjects effects revealed ADHD subtype differences on the means of PSQI and FSS, with significantly higher PSQI and FSS scores for ADHD-I patients (Table 3.5). Moreover, a statistically significant interaction between ADHD subtype and gender was found \(F_{3,119} = 3.70; p = 0.014; \text{partial } \varepsilon^2 = 0.085, \text{power to detect the effect} = 0.78; \text{Wilk’s lambda} = 0.92\]: FSS scores were higher for ADHD-I females than for ADHD-C females; while in males, FSS scores were comparable between subtypes (Table 3.6).
Table 3.5 Effects of ADHD subtype on daytime function, sleep quality, and fatigue

<table>
<thead>
<tr>
<th>Tests of Between-Subjects Effects</th>
<th>ADHD-I mean (SD)</th>
<th>ADHD-C mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>9.42 (±4.37)</td>
<td>9.92 (±4.62)</td>
</tr>
<tr>
<td>PSQI*</td>
<td>8.36 (±3.27)</td>
<td>7.24 (±2.95)</td>
</tr>
<tr>
<td>FSS*</td>
<td>4.51 (±1.40)</td>
<td>4.11 (±1.26)</td>
</tr>
</tbody>
</table>

Multivariate analysis of co-variance was conducted to compare scores on the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Fatigue Severity Scale (FSS) in ADHD Subtype and gender groups, while controlling for age. Significant multivariate effects were found for ADHD subtype x gender interaction (see table 3.6), and for ADHD subtype. As shown above, significant multivariate main effects for ADHD subtype were obtained for PSQI and FSS scores ($F_{3,119} = 4.47$, $p = 0.005$, partial $\epsilon^2 = 0.1$, power = 0.87, Wilk’s Lambda = 0.90).

* $p \leq 0.01$

Table 3.6 Effect of ADHD-subtype x gender interaction on fatigue severity scale

<table>
<thead>
<tr>
<th>Tests of Between-Subjects Effects</th>
<th>ADHD-I mean (SD)</th>
<th>ADHD-C mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>5.48 (±1.19)</td>
<td>3.71 (±1.12)</td>
</tr>
<tr>
<td>Males</td>
<td>4.12 (±1.35)</td>
<td>4.25 (±1.30)</td>
</tr>
</tbody>
</table>

Multivariate analysis of co-variance was conducted to compare scores on the Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Fatigue Severity Scale (FSS) in ADHD Subtype and gender groups, while controlling for age. Significant multivariate effects were found for ADHD subtype (see table 3.5), and for ADHD subtype x gender interaction. $F_{3,119} = 3.70$, $p = 0.014$, partial $\epsilon^2 = 0.085$, power = 0.78, Wilk’s Lambda = 0.92

* $p \leq 0.01$

Table 3.7 Pearson partial correlations for the relationships between each pair of questionnaires in ADHD subtypes

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>ADHD-I$^a$ n = 45</th>
<th>ADHD-C$^b$ n = 81</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>$r = -0.002$</td>
<td>$r = 0.113$</td>
</tr>
<tr>
<td>PSQI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSS</td>
<td>$r = 0.171$</td>
<td>$r = 0.305^*$</td>
</tr>
<tr>
<td>PSQI</td>
<td>$r = 0.413^*$</td>
<td>$r = 0.324^*$</td>
</tr>
</tbody>
</table>

Abbreviations: ESS – Epworth Sleepiness Scale; FSS – Fatigue Severity Scale; PSQI – Pittsburgh Sleep Quality Index.

* Significant correlations at $p = 0.01$
3.1.2.3 Relationships between subjective sleepiness, sleep quality and fatigue

A series of Pearson partial correlations between pairs of questionnaires corresponding to daytime sleepiness (ESS), sleep quality (PSQI), and fatigue (FSS) were conducted in ADHD-I and ADHD-C groups to determine: (a) whether there are underlying relationships between subjective reports of sleep quality and the perceptions of daytime sleepiness and fatigue, and (b) whether these underlying relationships differ between ADHD subtypes. Gender and age were controlled for in all partial correlations. Because three correlations were conducted per ADHD subtype group, the p-value was adjusted to 0.01. Two-tailed Pearson correlation coefficient critical values were then calculated for \( p = 0.01 \) using Microsoft Excel, which revealed that for a sample size of 45 – which was the case for the ADHD-I group – the critical value was 0.380; and that for a sample size of 80 – which was the case for the ADHD-C group – the critical value was 0.286. Following these guidelines, FSS correlated significantly with PSQI in ADHD-I subjects; and FSS correlated significantly with both PSQI and ESS in ADHD-C subjects (Table 3.7).

3.2 Phase II

While Phase I of the study was designed to examine subjective measures of sleep in a small sample of subjects representative of the general ADHD population, Phase II of the study was designed to conduct an in-depth and objective examination of sleep in subjects with ADHD with complaints of sleep problems. The data collected in this phase are presented in two sections. In section 3.2.1, I present data pertaining to circadian regulation of sleep-wake cycles to test

**Hypothesis 2**: The circadian regulation of sleep-wake cycles in ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality differs in ADHD-I and ADHD-C groups.

In section 3.2.2, I present data pertaining to the macrostructure of sleep to test **Hypothesis 3**: Objective measures of sleep in ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality differ in ADHD-I and ADHD-C groups.
3.2.1 Chronotypes and ADHD – Relationships between circadian preference, melatonin, and the core symptoms of ADHD

While there is evidence that abnormal circadian cycles are a significant clinical consideration in the sleep disturbances of ADHD, the effect that such abnormalities may have on ADHD symptomatology is not well understood. Moreover, whether there are differences in the regulation of circadian cycles in the subtypes of ADHD has hitherto not been explored. Thus, this segment of the study was conducted to examine the nature of the relationships between chronotype and the core symptoms of ADHD in an adult ADHD population with sleep complaints, and to determine whether the nature of such relationships differs in ADHD subtypes. To this end, subjective and objective measures of circadian phase and ADHD symptomatology were collected from and compared in 23 adults diagnosed with ADHD-I and 33 adults diagnosed with ADHD-C.

3.2.1.1 Demographics

Data were collected from 56 subjects (40 ±10 years of age, 28% female), of whom 23 had been diagnosed with ADHD-I (42 ± 12 years of age, 39% female) and 33 had been diagnosed with ADHD-C (38 ± 9 years of age, 21% female) (Table 3.8). ADHD subtype groups did not differ with respect to age \([F_{1,52} = 2.485, p = 0.121]\) or gender distribution \([\chi^2_{1,56} = 2.132, p = 0.144]\).

3.2.1.2 Subjective correlates of circadian phase

MEQ scores were used as subjective correlates of circadian phase (Table 3.8). Average MEQ scores were 16.52 ± 5.92 in ADHD-I and 15.45 ± 4.65 in ADHD-C. These values, which did not differ significantly in ADHD subtype groups \([F_{1,53} = 0.012, p = 0.91]\), indicate a predominance of intermediate to moderate evening chronotypes in adult ADHD.

To get a better idea of chronotype frequencies in ADHD, subjects were stratified according to MEQ scores. As such, 8 subjects were identified as moderately morning types, 19 were identified as intermediate types, 22 were identified as moderately evening types, and 7 were identified as definitely evening types (Table 3.8).
Table 3.8 Study subject demographics and subjective correlates of circadian phase in ADHD subtype groups

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (n = 56)</th>
<th>ADHD-I (n = 23)</th>
<th>ADHD-C (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age^a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>40 ± 10</td>
<td>42 ± 12</td>
<td>38 ± 9</td>
</tr>
<tr>
<td>Gender^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>16 (29%)</td>
<td>9 (39%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Males</td>
<td>40 (71%)</td>
<td>14 (61%)</td>
<td>26 (79%)</td>
</tr>
<tr>
<td>MEQ^c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>15.89 ± 5.19</td>
<td>16.52 ± 5.92</td>
<td>15.45 ± 4.65</td>
</tr>
<tr>
<td>Chronotype^d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately Morning</td>
<td>8 (14%)</td>
<td>5 (22%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>19 (34%)</td>
<td>8 (35%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Moderately Evening</td>
<td>22 (39%)</td>
<td>7 (30%)</td>
<td>15 (46%)</td>
</tr>
<tr>
<td>Definitely Evening</td>
<td>7 (13%)</td>
<td>3 (13%)</td>
<td>4 (12%)</td>
</tr>
</tbody>
</table>

Abbreviations: MEQ – morningness-eveningness questionnaire

^a F_{1,52} = 2.485, p = 0.121
^b X^2_{1,56} = 2.132, p = 0.144
^c F_{1,52} = 0.012, p = 0.914 (IV = subtype, CV = age and gender)

Table 3.9 Study subject demographics in morning (AM), intermediate (I), and evening (PM) chronotype groups

<table>
<thead>
<tr>
<th></th>
<th>AM (n = 8)</th>
<th>I (n = 19)</th>
<th>PM (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age^a,b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>50 ± 7</td>
<td>42 ± 9</td>
<td>35 ± 10</td>
</tr>
<tr>
<td>Gender^c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4 (50%)</td>
<td>5 (26%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Male</td>
<td>4 (50%)</td>
<td>14 (74%)</td>
<td>22 (76%)</td>
</tr>
<tr>
<td>ADHD subtype^d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD-I</td>
<td>5 (62.5%)</td>
<td>8 (42%)</td>
<td>10 (35%)</td>
</tr>
<tr>
<td>ADHD-C</td>
<td>3 (37.5%)</td>
<td>11 (58%)</td>
<td>19 (65%)</td>
</tr>
</tbody>
</table>

^a F_{2,53} = 8.2, p = 0.001
^b AM older than PM groups according to Bonferroni post-hoc tests, at p = 0.001
^c X^2_{2,56} = 2.13, p = 0.35
^d X^2_{2,56} = 2.05, p = 0.36

Subjects were then re-organized into three groups of comparison: those with moderate morning chronotype were denominated the Morning Group (AM), those with definite and moderate evening chronotypes were combined into the Evening Group (PM), and those with intermediate chronotype were denominated the Intermediate Group (I) (Table 3.9). These chronotype groups
were comparable in regards to gender \( \chi^2_{2,56} = 2.13, p = 0.35 \) and ADHD subtype \( \chi^2_{2,56} = 2.05, p = 0.36 \) distributions. Mean age, however, differed between groups \( F_{2,53} = 8.2, p = 0.001 \). The effect size, calculated using eta squared, was 0.21, and post-hoc comparisons using Bonferroni indicated that the AM group was significantly older than the PM group \( p = 0.001 \).

### 3.2.1.3 Objective correlates of circadian phase

Salivary samples were collected from study subjects at hourly intervals from 19:00 h to 02:00 h to assay endogenous melatonin secretion profiles. DLMO, set as the first time at which salivary melatonin reaches a minimum concentration of 4 pg/ml, was used as an objective correlate of circadian phase. Two-way ANCOVA was conducted to compare ranked DLMO values in ADHD subtype groups and in chronotype groups. The analysis revealed no significant ADHD subtype differences \( F_{1,47} = 2.61, p = 0.11 \) (Table 3.10); and statistically significant chronotype group differences \( F_{2,47} = 6.19, p = 0.004, \text{partial } \epsilon^2 = 0.21, \text{ power to detect } = 0.87 \) (Table 3.11). Specifically, Bonferroni post-hoc tests revealed that DLMO occurred significantly later in the PM group \( 22:25 \pm 01:41 \text{ hh:mm} \) than in the AM \( 20:45 \pm 00:43 \text{ hh:mm}, p = 0.03 \) and I \( 20:53 \pm 01:02 \text{ hh:mm}, p = 0.005 \) groups.

<table>
<thead>
<tr>
<th>DLMO time(^a)</th>
<th>TOTAL ((n = 56))</th>
<th>ADHD-I ((n = 23))</th>
<th>ADHD-C ((n = 33))</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean ± SD (hh:mm)</td>
<td>21:40 ± 01:35</td>
<td>20:53 ± 01:02</td>
<td>22:25 ± 01:41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DLMO timing(^b)</th>
<th>Non-DGPS</th>
<th>DSPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>43 (77%)</td>
<td>19 (83%)</td>
</tr>
<tr>
<td>13 (23%)</td>
<td>4 (17%)</td>
<td>9 (27%)</td>
</tr>
</tbody>
</table>

**Table 3.10 Objective correlates of circadian phase in ADHD subtype groups**

**Abbreviations:** DLMO – dim light melatonin onset; DSPS – delayed sleep phase syndrome; non-DGPS – non-delayed sleep phase syndrome.

\(^a\) \( F_{1,47} = 2.614, p = 0.113 \)

\( \chi^2_{1,56} = 0.14, p = 0.71 \)
Table 3.11 Objective correlates of circadian phase in morning (AM), intermediate (I), and evening (PM) chronotype groups

<table>
<thead>
<tr>
<th></th>
<th>AM (n = 8)</th>
<th>I (n = 19)</th>
<th>PM (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DLMO time</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD (hh:mm)</td>
<td>20:45 ± 00:43</td>
<td>20:53 ± 01:02</td>
<td>22:25 ± 01:41</td>
</tr>
<tr>
<td><strong>DLMO timing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DSPS</td>
<td>8 (100%)</td>
<td>17 (89.5%)</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>DSPS</td>
<td>0 (100%)</td>
<td>2 (10.5%)</td>
<td>11 (38%)</td>
</tr>
</tbody>
</table>

\( ^a F_{2,47} = 6.192, p = 0.004, \text{ partial } \varepsilon^2 = 0.209, \text{ power} = 0.872. \) DLMO occurred significantly later in the PM group than in the AM (\( p = 0.03 \)) and I (\( p = 0.005 \)) groups

\( ^b X^2_{2,56} = 7.26, p = 0.03 \)

The use of DLMO tests as markers of circadian phase have been documented. In studies of melatonin secretion profiles, average DLMO times of 20:50 ± 01:12 hrs (Burgess & Fogg, 2008) and 20:35 ± 01:08 hrs (Rahman et al., 2009) have been reported for healthy populations; and average DLMO times of 23:10 ± 02:18 hrs (Nagtegaal et al., 1998) and 23:06 ± 01:43 hrs (Rahman et al., 2009) have been reported in subjects with DSPS. Together, these studies suggest that DLMO occurs approximately between 19:30 and 22:00 hrs in healthy populations (Pandi-Perumal et al., 2007), and between 21:00 and 02:30 in subjects with DSPS. Based on the combined data of these studies, the 22:00 h mark was chosen as a cut-off, and DLMO test results were used to dichotomize the subjects of this study as either DSPS or non-DSPS: the non-DSPS group was composed of subjects with DLMO between 19:00 h and 22:00 h, and the DSPS group was composed of subjects with DLMO at 23:00h or later. DSPS and non-DSPS subject frequencies were comparable in ADHD subtype groups \( [X^2_{1,56} = 0.14, p = 0.71] \) (Table 3.10). On the other hand, DSPS and non-DSPS subject frequencies differed significantly in chronotype groups \( [X^2_{2,56} = 7.26, p = 0.03] \), with the PM group having the highest proportion of subjects classified as DSPS (Table 3.11).

3.2.1.4 ADHD symptoms and circadian preference

Pearson partial correlations between the ranked values of DLMO, MEQ scores, and the T-scores for CAARS subscales corresponding to DSM-IV-I and DSM-IV-H/I were conducted to determine whether subjective circadian preference and DLMO are related to the severity of the
core symptoms of ADHD in the Inattentive and Combined subtypes of ADHD. Because five partial correlations were conducted per ADHD subtype group, the p-value was adjusted to 0.01. Two-tailed Pearson correlation coefficient critical values were then calculated for $p = 0.01$ using Microsoft Excel, which revealed that for a sample size of 23 – which was the case for the ADHD-I group – the critical value was 0.526; and that for a sample size of 35 – which was the case for the ADHD-C group – the critical value was 0.430. Following these guidelines, it was found that the relationships between ranked values of DLMO, MEQ, and ADHD symptom severity differed between subtypes (Table 3.12). Specifically, it was found that the only statistically significant correlation in ADHD-I subjects was that of DLMO with DSM-IV-I ($r = 0.501$). On the other hand, ADHD-C subjects had statistically significant correlations between DLMO and MEQ ($r = 0.696$), between DLMO and DSM-IV-H/I ($r = 0.438$), and between MEQ and DSM-IV-H/I ($r = 0.470$).

<table>
<thead>
<tr>
<th></th>
<th>ADHD-I n = 23</th>
<th>ADHD-C n = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DLMO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEQ</td>
<td>$r = -0.339$</td>
<td>$r = -0.629^*$</td>
</tr>
<tr>
<td>DSM-IV-I</td>
<td>$r = 0.501^*$</td>
<td>$r = -0.368$</td>
</tr>
<tr>
<td>DSM-IV-H/I</td>
<td>$r = -0.442$</td>
<td>$r = -0.438^*$</td>
</tr>
<tr>
<td><strong>MEQ</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-IV-I</td>
<td>$r = -0.160$</td>
<td>$r = 0.051$</td>
</tr>
<tr>
<td>DSM-IV-H/I</td>
<td>$r = 0.404$</td>
<td>$r = 0.470^*$</td>
</tr>
</tbody>
</table>


* Significant correlations at $p = 0.01$

### 3.2.2 Objective measures of sleep

Sleep was recorded over the course of two nights by means of polysomnography. Data were collected from 68 subjects, of whom 27 were of the ADHD-I subtype (19-59 years of age, mean $39 \pm 12$ years of age, 33% females) and 41 were of the ADHD-C subtype (21-55 years of age, $37 \pm 9$ years of age, 20% females). There were no significant differences with respect to mean
age \( [F_{1,66} = 0.41, \ p = 0.52] \) or gender distribution \( [\chi^2_{1,66} = 1.66, \ p = 0.20] \) between the two groups.

### 3.2.2.1 Macrostructure of sleep

Means and standard deviations of PSG parameters of sleep for the first and second nights of recordings are displayed in Table 3.13. Given the significant correlations found between DLMO time and the core symptoms of ADHD in section 3.2.1.4, a repeated-measures MANCOVA controlling for gender and the ranked values of age and DLMO time was conducted to examine the effects of ADHD subtype and night of recording on PSG parameters of sleep. This analysis revealed no significant differences between values collected on the first and second nights of recordings \( [F_{14, 30} = 1.99, \ p = 0.06] \), no significant differences between ADHD subtypes \( [F_{14, 30} = 1.81, \ p = 0.09] \), and no significant night x ADHD subtype interactions \( [F_{14, 30} = 0.58, \ p = 0.86] \).

As evidenced by the high standard deviations, indices of respiratory (AHI) and movement related events (PLMI) were variable in the study subjects, regardless of ADHD subtype. In the clinical setting, AHI and PLMI values are used to diagnose and determine the severity of SDB and PLMS. AHI > 5 and PLMI > 5 are generally considered to be abnormal (Young et al., 1993; Bae & Foldvary-Schaefer, 2004; Scofield et al., 2008). Moreover, AHI values between 5 and 15 denote mild SDB, values between 15 and 30 denote moderate SDB, and values of over 30 denote severe SDB. Similarly, PLMI values between 5 and 25 denote mild PLMS, values between 25 and 50 denote moderate PLMS, and values of over 50 denote severe PLMS. These guidelines were used to stratify the subjects of this study according to severity of SDB and PLMS.

As displayed in Table 3.14, 63.2% of ADHD subjects had normal PLMI, 26.5% of subjects met the criterion for mild PLMS, and 10.3% met the criterion for moderate PLMS. For respiratory-related events, 77.9% of ADHD subjects had normal AHI, 11.8% met the criterion for mild SDB, 7.4% met the criterion for moderate SDB, and 2.9% met the criterion for severe SDB. These values remained relatively stable after stratifying the data into subjects diagnosed with ADHD-I and ADHD-C, and a chi-squared test revealed that the Inattentive and Combined
ADHD groups did not differ with respect to the distribution of subjects with normal, mild, moderate, or severe PLMS [$\chi^2_{2,68} = 1.46, p = 0.48$] and SDB [$\chi^2_{3,68} = 2.19, p = 0.53$].

Table 3.13 Summary polysomnography measures

<table>
<thead>
<tr>
<th></th>
<th>TOTAL (n = 68)</th>
<th>ADHD-I (n = 27)</th>
<th>ADHD-C (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST (minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>356.6 ± 73.0</td>
<td>374.0 ± 71.5</td>
<td>345.2 ± 72.6</td>
</tr>
<tr>
<td>Second Night</td>
<td>408.4 ± 81.1</td>
<td>414.0 ± 70.2</td>
<td>404.3 ± 89.3</td>
</tr>
<tr>
<td>SE (percentage)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>77.6 ± 15.8</td>
<td>81.4 ± 15.3</td>
<td>75.0 ± 15.8</td>
</tr>
<tr>
<td>Second Night</td>
<td>84.3 ± 12.2</td>
<td>85.8 ± 8.8</td>
<td>83.2 ± 14.3</td>
</tr>
<tr>
<td>SOL (minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>39.2 ± 48.5</td>
<td>30.3 ± 34.7</td>
<td>45.1 ± 55.3</td>
</tr>
<tr>
<td>Second Night</td>
<td>20.6 ± 26.4</td>
<td>20.0 ± 20.0</td>
<td>21.1 ± 30.8</td>
</tr>
<tr>
<td>REM Latency (minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>101 ± 63</td>
<td>93 ± 54</td>
<td>106 ± 68</td>
</tr>
<tr>
<td>Second Night</td>
<td>90 ± 52</td>
<td>88 ± 53</td>
<td>92 ± 53</td>
</tr>
<tr>
<td>Awakenings (minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>18 ± 10</td>
<td>14 ± 8</td>
<td>21 ± 10</td>
</tr>
<tr>
<td>Second Night</td>
<td>18 ± 13</td>
<td>14 ± 7</td>
<td>21 ± 15</td>
</tr>
<tr>
<td>REM Periods (minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>4 ± 1</td>
<td>3 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Second Night</td>
<td>5 ± 8</td>
<td>6 ± 12</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Percentage of TST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>6.4 ± 4.7</td>
<td>4.8 ± 2.6</td>
<td>7.5 ± 5.5</td>
</tr>
<tr>
<td>Second Night</td>
<td>5.9 ± 3.3</td>
<td>5.3 ± 2.8</td>
<td>6.4 ± 3.6</td>
</tr>
<tr>
<td>Stage 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>53.9 ± 7.7</td>
<td>54.9 ± 8.1</td>
<td>53.3 ± 7.4</td>
</tr>
<tr>
<td>Second Night</td>
<td>53.9 ± 9.5</td>
<td>53.7 ± 8.2</td>
<td>54.1 ± 10.4</td>
</tr>
<tr>
<td>SWS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>18.8 ± 8.1</td>
<td>19.5 ± 7.4</td>
<td>18.3 ± 8.6</td>
</tr>
<tr>
<td>Second Night</td>
<td>17.9 ± 7.8</td>
<td>18.1 ± 6.9</td>
<td>17.7 ± 8.4</td>
</tr>
<tr>
<td>REM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>20.8 ± 6.4</td>
<td>20.7 ± 7.9</td>
<td>20.9 ± 5.4</td>
</tr>
<tr>
<td>Second Night</td>
<td>22.3 ± 6.8</td>
<td>22.9 ± 7.2</td>
<td>21.8 ± 6.5</td>
</tr>
<tr>
<td>AHI in TST (events/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>5.6 ± 14.2</td>
<td>4.2 ± 7.0</td>
<td>6.5 ± 17.4</td>
</tr>
<tr>
<td>Second Night</td>
<td>3.6 ± 8.6</td>
<td>2.8 ± 5.5</td>
<td>4.1 ± 10.5</td>
</tr>
<tr>
<td>PLMI in TST (events/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>8.1 ± 11.9</td>
<td>7.9 ± 12.7</td>
<td>8.2 ± 11.5</td>
</tr>
<tr>
<td>Second Night</td>
<td>10.6 ± 13.2</td>
<td>10.9 ± 14.0</td>
<td>10.4 ± 12.8</td>
</tr>
<tr>
<td>Indices of arousal in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST (events/h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>3.1 ± 8.3</td>
<td>1.8 ± 3.1</td>
<td>3.9 ± 10.4</td>
</tr>
<tr>
<td>Second Night</td>
<td>2.1 ± 5.3</td>
<td>1.2 ± 1.9</td>
<td>2.9 ± 6.8</td>
</tr>
<tr>
<td>PLMA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>1.9 ± 3.2</td>
<td>1.6 ± 3.0</td>
<td>2.1 ± 3.3</td>
</tr>
<tr>
<td>Second Night</td>
<td>3.1 ± 4.3</td>
<td>2.6 ± 3.7</td>
<td>3.4 ± 4.8</td>
</tr>
<tr>
<td>RERA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>2.5 ± 7.9</td>
<td>0.8 ± 1.4</td>
<td>3.6 ± 10.0</td>
</tr>
<tr>
<td>Second Night</td>
<td>1.2 ± 2.4</td>
<td>1.3 ± 2.8</td>
<td>1.2 ± 2.1</td>
</tr>
<tr>
<td>Spont.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Night</td>
<td>13.5 ± 6.1</td>
<td>12.6 ± 5.9</td>
<td>14.2 ± 6.2</td>
</tr>
<tr>
<td>Second Night</td>
<td>12.9 ± 6.7</td>
<td>13.0 ± 7.3</td>
<td>12.9 ± 6.4</td>
</tr>
</tbody>
</table>

Abbreviations: AHA = apnea/hypopnea related arousals; AHI = apnea/hypopnea index; NREM = non-rapid eye movement sleep; PLMA = periodic limb movement related arousal; PLMI = periodic limb movement index; REM = rapid eye movement; RERA = respiratory event related arousal; SE = sleep efficiency; SOL = sleep onset latency; SWS = slow wave sleep; TST = total sleep time.
### Table 3.14 Distribution of PLMI and AHI

<table>
<thead>
<tr>
<th>Movement related events</th>
<th>TOTAL</th>
<th>ADHD-I</th>
<th>ADHD-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (PLMI &lt; 5)</td>
<td>43 (63.2%)</td>
<td>19 (70.4%)</td>
<td>24 (58.5%)</td>
</tr>
<tr>
<td>Mild PLMS (5 ≤ PLMI &lt; 25)</td>
<td>18 (26.5%)</td>
<td>5 (18.5%)</td>
<td>13 (31.7%)</td>
</tr>
<tr>
<td>Moderate PLMS (25 ≤ PLMI &lt; 50)</td>
<td>7 (10.3%)</td>
<td>3 (11.1%)</td>
<td>4 (9.8%)</td>
</tr>
<tr>
<td>Severe PLMS (PLMI ≥ 50)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory events</th>
<th>No SDB (AHI &lt; 5)</th>
<th>Mild SDB (5 ≤ AHI &lt; 15)</th>
<th>Moderate SDB (15 ≤ AHI &lt; 30)</th>
<th>Severe SDB (AHI ≥ 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (PLMI &lt; 5)</td>
<td>53 (77.9%)</td>
<td>8 (11.8%)</td>
<td>5 (7.4%)</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>Mild SDB (5 ≤ AHI &lt; 15)</td>
<td>21 (77.8%)</td>
<td>3 (11.1%)</td>
<td>3 (11.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Moderate SDB (15 ≤ AHI &lt; 30)</td>
<td>32 (78%)</td>
<td>5 (12.2%)</td>
<td>2 (4.9%)</td>
<td>2 (4.9%)</td>
</tr>
</tbody>
</table>

Abbreviations: AHI – Apnea/hypopnea index; PLMI – periodic limb movement index; PLMS – periodic limb movement in sleep; SDB – sleep-disordered breathing.

### 3.2.2.2 PSG parameters of sleep and the core symptoms of ADHD

In order to investigate how sleep relates to the core symptoms of ADHD in ADHD subtypes, Pearson partial correlations were conducted between CAARS subscales corresponding to Inattention/Memory Problems, Hyperactivity/Restlessness, and Impulsivity/Emotional Lability and PSG parameters of sleep architecture, arousal, and respiratory and movement related events in ADHD-I and ADHD-C subtypes while controlling for age, gender, and DLMO time. Because 14 partial correlations were conducted per ADHD subtype group, the p-value was adjusted to 0.002. Two-tailed Pearson correlation coefficient critical values were then calculated for p = 0.002 using Microsoft Excel, which revealed that for a sample size of 27 – which was the case for the ADHD-I group – the critical value was 0.567; and that for a sample size of 41 – which was the case for the ADHD-C group – the critical value was 0.468. Following these guidelines, it was found that the relationships between PSG measures of sleep and ADHD symptom severity differed between subtypes (Table 3.15). Specifically, it was found that in ADHD-I subjects, symptoms of Inattention/Memory Problems correlated significantly with RERA; while correlations of Hyperactivity/Restlessness with awakenings, with SWS percentage, and with spontaneous arousal index approached significance. For ADHD-C subjects, symptoms of Hyperactivity/Restlessness correlated significantly with REM sleep latency and with awakenings, and symptoms of Impulsivity/Emotional Lability correlated significantly with awakenings and with AHA; while correlations of Inattentio
Hyperactivity/Restlessness and REM sleep percentage, and Impulsivity/Emotional Lability and SWS percentage approached significance.

Table 3.15 Correlations between PSG measures of sleep and the core symptoms of ADHD

<table>
<thead>
<tr>
<th>PSG PARAMETER</th>
<th>CAARS-A</th>
<th>CAARS-B</th>
<th>CAARS-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD-I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>r = 0.211</td>
<td>r = -0.073</td>
<td>r = 0.059</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>r = 0.084</td>
<td>r = -0.359</td>
<td>r = -0.153</td>
</tr>
<tr>
<td>Sleep Onset Latency</td>
<td>r = 0.207</td>
<td>r = 0.116</td>
<td>r = 0.418</td>
</tr>
<tr>
<td>REM Sleep Latency</td>
<td>r = -0.157</td>
<td>r = 0.106</td>
<td>r = 0.298</td>
</tr>
<tr>
<td>Awakenings</td>
<td>r = -0.087</td>
<td>r = 0.515*</td>
<td>r = 0.214</td>
</tr>
<tr>
<td>REM Periods</td>
<td>r = -0.015</td>
<td>r = 0.064</td>
<td>r = -0.416</td>
</tr>
<tr>
<td>Stage 1 %</td>
<td>r = -0.060</td>
<td>r = -0.034</td>
<td>r = 0.489</td>
</tr>
<tr>
<td>Stage 2 %</td>
<td>r = 0.002</td>
<td>r = 0.423</td>
<td>r = -0.457</td>
</tr>
<tr>
<td>Slow Wave Sleep %</td>
<td>r = -0.196</td>
<td>r = 0.559*</td>
<td>r = 0.176</td>
</tr>
<tr>
<td>REM sleep %</td>
<td>r = 0.279</td>
<td>r = 0.177</td>
<td>r = 0.136</td>
</tr>
<tr>
<td>PLMA</td>
<td>r = -0.226</td>
<td>r = -0.069</td>
<td>r = 0.476</td>
</tr>
<tr>
<td>AHA</td>
<td>r = -0.029</td>
<td>r = -0.274</td>
<td>r = 0.322</td>
</tr>
<tr>
<td>RERA</td>
<td>r = 0.584*</td>
<td>r = 0.193</td>
<td>r = 0.192</td>
</tr>
<tr>
<td>SA</td>
<td>r = 0.448</td>
<td>r = 0.514*</td>
<td>r = 0.174</td>
</tr>
<tr>
<td>ADHD-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Sleep Time</td>
<td>r = 0.127</td>
<td>r = 0.059</td>
<td>r = 0.135</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>r = 0.148</td>
<td>r = -0.136</td>
<td>r = 0.004</td>
</tr>
<tr>
<td>Sleep Onset Latency</td>
<td>r = 0.275</td>
<td>r = 0.121</td>
<td>r = 0.200</td>
</tr>
<tr>
<td>REM Sleep Latency</td>
<td>r = -0.134</td>
<td>r = 0.528*</td>
<td>r = 0.262</td>
</tr>
<tr>
<td>Awakenings</td>
<td>r = 0.224</td>
<td>r = 0.510*</td>
<td>r = 0.507*</td>
</tr>
<tr>
<td>REM Periods</td>
<td>r = 0.110</td>
<td>r = 0.008</td>
<td>r = 0.079</td>
</tr>
<tr>
<td>Stage 1 %</td>
<td>r = -0.104</td>
<td>r = 0.355</td>
<td>r = 0.339</td>
</tr>
<tr>
<td>Stage 2 %</td>
<td>r = -0.041</td>
<td>r = -0.001</td>
<td>r = 0.121</td>
</tr>
<tr>
<td>Slow Wave Sleep %</td>
<td>r = -0.045</td>
<td>r = 0.062</td>
<td>r = -0.419*</td>
</tr>
<tr>
<td>REM sleep %</td>
<td>r = -0.180</td>
<td>r = -0.499*</td>
<td>r = -0.168</td>
</tr>
<tr>
<td>PLMA</td>
<td>r = -0.447*</td>
<td>r = -0.171</td>
<td>r = -0.306</td>
</tr>
<tr>
<td>AHA</td>
<td>r = 0.279</td>
<td>r = 0.181</td>
<td>r = 0.473*</td>
</tr>
<tr>
<td>RERA</td>
<td>r = 0.207</td>
<td>r = -0.141</td>
<td>r = -0.005</td>
</tr>
<tr>
<td>SA</td>
<td>r = 0.097</td>
<td>r = -0.021</td>
<td>r = 0.140</td>
</tr>
</tbody>
</table>

Abbreviations: AHA – apnea/hypopnea related arousals; PLMA – periodic limb movement related arousal; REM – rapid eye movement; RERA – respiratory event related arousal; SA – spontaneous arousal index.

* Correlations significant at or approaching significance at p = 0.01
3.3 Summary of results

_Hypothesis 1:_ Subjective correlates of sleep such as daytime sleepiness, fatigue, and sleep quality differ in adults diagnosed with ADHD-I and adults diagnosed with ADHD-C.

**Results:** Sleep quality and fatigue were worse for ADHD-I than for ADHD-C subjects. Moreover, while fatigue correlated with sleep quality in both ADHD subtypes, the ADHD-C group was also characterized by a significant correlation between sleepiness and fatigue. Thus, the null hypothesis is rejected.

_Hypothesis 2:_ In ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality, the circadian regulation of sleep-wake cycles differs in ADHD-I and ADHD-C groups. In this regard:

_Hypothesis 2a:_ Correlates of circadian phase such as subjective circadian preference and melatonin secretion profiles differ in ADHD-I and ADHD-C groups.

**Results:** Neither subjective nor objective correlates of circadian phase differed in ADHD-I and ADHD-C groups. Thus, the null hypothesis cannot be rejected.

_Hypothesis 2b:_ Associations between correlates of circadian phase and the core symptoms of ADHD differ in ADHD-I and ADHD-C groups.

**Results:** The relationships between circadian preference, DLMO time, and ADHD symptoms differed in ADHD subtypes. In ADHD-I, inattention scores correlated with DLMO time but not with MEQ scores. In ADHD-C, hyperactivity/impulsivity scores correlated with DLMO time and with MEQ scores. Thus, the null hypothesis is rejected.

_Hypothesis 3:_ In ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality, objective measures of sleep differ in ADHD-I and ADHD-C groups. In this regard:
**Hypothesis 3a:** The macrostructure of sleep differs in ADHD-I and ADHD-C groups.

**Results:** There were no significant differences in PSG variables of sleep macrostructure between ADHD groups or between the first and second nights of recordings. Thus, the null hypothesis cannot be rejected.

**Hypothesis 3b:** The prevalence of sleep-disordered breathing differs in ADHD-I and ADHD-C groups.

**Results:** The occurrence of respiratory events was comparable between ADHD subtypes. Thus, the null hypothesis cannot be rejected.

**Hypothesis 3c:** The prevalence of periodic limb movements in sleep differs in ADHD-I and ADHD-C groups.

**Results:** The occurrence of periodic limb movement events was comparable between ADHD subtypes. Thus, the null hypothesis cannot be rejected.

**Hypothesis 3d:** Associations between objective measures of sleep and the core symptoms of ADHD differ in ADHD-I and ADHD-C groups.

**Results:** Associations between objective measures of sleep and the core symptoms of ADHD differed in ADHD-I and ADHD-C groups. In ADHD-I, Inattention/Memory Problems correlated significantly with RERA. In ADHD-C, Hyperactivity/Restlessness correlated significantly with REM sleep latency and with awakenings, and Impulsivity/Emotional Lability correlated significantly with awakenings and with AHA. Thus, the null hypothesis is rejected.
Chapter 4
DISCUSSION

In the sections that follow, I will discuss the results presented in this dissertation. In section 4.1, I will discuss the results corresponding to the data collected for Phase I of the study, that is, subjective assessment of sleep in adults with ADHD of the Inattentive and Combined subtypes by means of the questionnaires: ESS, PSQI, and FSS. In section 4.2, I will discuss the results corresponding to the data collected for Phase II of the study, that is, objective assessment of sleep in adults with ADHD of the Inattentive and Combined subtypes by means of PSG and DLMO studies.

4.1 Phase I

4.1.1 Characterization of study subjects

The subjects of this study were characterized by high inattention scores; and by average Reward Dependence and Cooperativeness, Low Persistence, and very low Self-Directedness regardless of ADHD subtype (Table 3.1). On the other hand, measures of Hyperactivity/Impulsivity, Novelty Seeking Behaviour, Harm Avoidance, and Self-Transcendence differed significantly between ADHD subtype groups. These findings suggest that high Harm Avoidance and low Self-Transcendence are part of the ADHD-I phenotype; and that high Novelty Seeking and Hyperactivity/Impulsivity are part of the ADHD-C phenotype. For an in-depth discussion of putative mechanisms underlying these personality traits and symptoms profiles, please refer to Appendix VIII.

4.1.2 Subjective correlates of sleep

This section of the study was conducted to test *Hypothesis 1: Subjective correlates of sleep such as daytime sleepiness, fatigue, and subjective sleep quality differ in adults diagnosed with*
ADHD-I and adults diagnosed with ADHD-C. The results presented in Section 3.1.2 are discussed in the sections that follow.

4.1.2.1 Sleepiness, sleep quality, and fatigue in ADHD

In this population of adults with ADHD, a large proportion of subjects had complaints of poor sleep quality, excessive daytime sleepiness, and fatigue. Although data for age and gender matched healthy controls were not collected in this study, a review of the literature on normative data for PSQI, ESS, and FSS suggests that sleep quality, sleepiness, and fatigue are worse for ADHD subjects than for healthy controls of relatively comparable age ranges. As shown in Table 4.1, the reported means for normal controls were 3.5 to 7.5 for ESS, 3.9 to 5.4 for PSQI, and 1.7 to 2.3 for FSS. One sample t-tests comparing the results of this study to the values reported in the studies listed in Table 4.1 yielded statistically significant differences for all the values at p < 0.001, suggesting that sleep disorders pose a significant problem for adults with ADHD, thus making the management of sleep problems a desirable component of ADHD treatment.

Table 4.1 Normative data for ESS, PSQI, and FSS

<table>
<thead>
<tr>
<th>Scale</th>
<th>Mean ± SD for this study</th>
<th>Mean ± SD for other studies</th>
<th>n</th>
<th>Age (years)</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESS</td>
<td>9.74 ± 4.52</td>
<td>4.6 ± 2.8</td>
<td>72</td>
<td>22 -59</td>
<td>John and Hocking, 1997</td>
</tr>
<tr>
<td></td>
<td>4.5 ± 3.3</td>
<td>188</td>
<td>49 ± 16</td>
<td>Parkes et al., 1998</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.9 ± 3.8</td>
<td>174</td>
<td>64 ± 10</td>
<td>Ferreira et al., 2006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 ± 3.9</td>
<td>100</td>
<td>20 -69</td>
<td>Geisler et al., 2006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.5 ± 2.2</td>
<td>12</td>
<td>32 ± 10</td>
<td>Neu et al., 2008</td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td>7.64 ± 3.10</td>
<td>5.4 ± 3.3</td>
<td>174</td>
<td>64 ± 10</td>
<td>Ferreira et al., 2006</td>
</tr>
<tr>
<td></td>
<td>3.9 ± 2.2</td>
<td>100</td>
<td>20 -69</td>
<td>Geisler et al., 2006</td>
<td></td>
</tr>
<tr>
<td>FSS</td>
<td>4.25 ± 1.32</td>
<td>2.3 ± 0.7</td>
<td>20</td>
<td>40 ± 9</td>
<td>Krupp et al., 1989</td>
</tr>
<tr>
<td></td>
<td>1.7 ± 1.1</td>
<td>12</td>
<td>32 ± 10</td>
<td>Neu et al., 2008</td>
<td></td>
</tr>
</tbody>
</table>
4.1.2.2 Subjective correlates of sleep differ in adults with ADHD-I and adults with ADHD-C

Sleep quality and fatigue were worse for ADHD-I than for ADHD-C patients (Table 3.5). Interestingly, I found that regardless of ADHD subtype, sleep quality was associated with fatigue but not with sleepiness, suggesting that in ADHD, fatigue may be a better predictor of poor sleep quality than sleepiness. In turn, sleepiness was associated with fatigue in ADHD-C but not in ADHD-I patients (Figure 4.1).

Figure 4.1 Interplay of sleep quality, sleepiness, and fatigue in ADHD subtypes

The idea that fatigue may be a better indicator of poor sleep quality than sleepiness has previously been explored, as studies in our laboratory have shown that subjects with insomnia have severe complaints of fatigue but normal sleepiness (Hossain et al., 2005), and that when subjects with sleep disorders are treated, changes in the ratings of quality of life correlate with changes in the ratings of fatigue, but not sleepiness (Hossain et al., 2007).

4.1.2.2.1 Sleep quality, sleepiness, and fatigue in ADHD-C

Sleepiness is defined as an increased propensity to doze off or fall asleep (Curcio et al., 2001) and fatigue is described as a feeling of tiredness, strain, or exhaustion that is associated with “…failure to initiate or sustain attentional tasks and physical activities requiring self-
motivation…” (Chaudhuri & Behan, 2000). While both sleepiness and fatigue are common symptoms of poor sleep quality or sleep deprivation (Hossain et al., 2005), the manifestation of these symptoms can arise from neurological mechanisms that are unrelated to sleep quality. For example, increased sleep propensity in a narcoleptic patient stems from deficits in orexin signaling rather than sleep deprivation (although poor sleep quality is likely to contribute to sleepiness) (Chemelli et al., 1999; Peyron et al., 2000; Thanickal et al., 2000), and cumulative evidence suggests that the manifestation of fatigue can stem from complex interactions that involve multiple etiological factors (Ohayon & Shapiro, 2000; Leavitt & DeLuca, 2010). As reviewed by Leavitt & DeLuca (2010), various models of fatigue have been proposed, such as immune system dysregulation, impaired nerve conduction, neuroendocrine and neurotransmitter dysregulation, and energy depletion theories. The multiplicity of models attempting to explain fatigue is likely a reflection of the existence of different subtypes of fatigue, each associated with a specific pathophysiology and set of etiological factors. The fact that for the ADHD-C subjects in this study, fatigue correlated with both sleep quality and sleepiness, while sleep quality and sleepiness did not correlate suggests that these ADHD-C patients were composed of at least two types of subjects: (i) those for whom fatigue was the result of poor sleep quality (and thus the correlation between FSS and PSQI), and (ii) those for whom fatigue was the result of an unknown variable that manifested in association with sleepiness (and thus the correlation between FSS and ESS). Regarding this second set of subjects, given that FSS and ESS correlated in ADHD-C but not ADHD-I subjects, and that ESS did not correlate with PSQI, I speculate that the correlation between sleepiness and fatigue has more to do with the neurological makeup of the ADHD-C patient and less to do with sleep quality.

Although the neurological mechanisms underlying the ADHD-C phenotype are not well understood, there is evidence in the literature and in the findings presented thus far that suggest that the ADHD-C subtype is associated with increased neuronal activity. In this regard, characteristics such as Hyperactivity, Impulsivity, and high Novelty Seeking Behaviour – which are exclusively associated with the ADHD-C subtype (Table 3.1) – have been posited to stem from overactivity in the striatum as a result of low tonic/high phasic DA secretion (as discussed in section 1.2.3.3.3), and from reduced D₂ autoreceptor activity in the SN/VTA (Zald et al., 2008; Tournier et al., 2013; see Appendix VIII for more details on this point). Interestingly, increased neuronal activity is associated with the accumulation of AD, as energy stocks in the
form of ATP are used up with increased cellular metabolic demands (Scharf et al., 2008; Porkka-Heiskanen & Kalinchuk, 2011). As discussed in section 1.3.3.2, AD plays roles in the monitoring of cellular energy stores, and concentrations increase with increased neuronal activity, strenuous exercise, or with sleep deprivation (Dworak et al., 2007). In the basal forebrain, hypothalamus and pons, activation of AD receptors leads to inhibition of neurons that promote wakefulness and, thus, to the onset of sleep (Porkka-Heiskanen et al., 2011). As a result, the aftermath of increased neuronal activity – which may very well be perceived as fatigue – may be an increased propensity to fall asleep and, in this respect, the experiences of fatigue and daytime sleepiness are expected to be associated with one another. Thus, in interpreting the finding that for my ADHD-C subjects, ESS correlated with FSS, but ESS did not correlate with PSQI, I propose that in a subset of my study ADHD-C subjects, the experience of severe sleepiness and fatigue is a result of overactive neurophysiological processes exclusively associated with the ADHD-C subtype rather than the quality of sleep.

4.1.2.2.2 Sleep quality, sleepiness, and fatigue in ADHD-I

In ADHD-I subjects, fatigue only correlated with sleep quality. Given that the perceptions of sleep quality and fatigue were worse for the ADHD-I group, it is possible that the poorer sleep quality in these subjects may have led to the heightened perception of fatigue. However, examination of the individual components of PSQI demonstrated that basic measures of sleep such as bedtime, rise time, SOL, and TST (Table 3.2); as well as the types and number of sleep problems afflicting subjects (Tables 3.3 and 3.4) were comparable in Inattentive and Combined subjects. Nevertheless, the rating for sleep was worse for ADHD-I than for ADHD-C patients. Given that the assessment of sleep quality and fatigue was conducted via subjective methodologies (self-reported questionnaires), it is possible that, contrary to the common expectation that poor sleep quality leads to fatigue, the heightened perception of fatigue in ADHD-I may have rendered these subjects more cognizant of sleep issues, which may in turn have made them more prone to overestimate their sleep problems and thus report low sleep ratings. Alternatively, it is possible that the poorer sleep ratings stem from an additional factor (not covered by PSQI) that worsens the perception of sleep quality in ADHD-I patients. One possibility is that some ADHD-I patients may suffer from non-restorative sleep (NRS). NRS is
sleep that is subjectively experienced as unrefreshing, restless, or of poor quality despite having received sufficient sleep (Wilkinson & Shapiro, 2012). Although NRS is often treated as a symptom of another primary sleep or medical disorder, there is evidence to suggest that NRS may be a syndrome in itself and, thus, a patient may present with NRS but no other sleep disorders or complaints (Wilkinson & Shapiro, 2012).

Although NRS is difficult to define using objective data, recent neurobiological models of insomnia have shed some light into possible mechanisms underlying NRS. Advances in sleep research indicate that sleep and wakefulness are processes regulated at a local level (Huber et al., 2004; Krueger et al., 2008; Nir et al., 2011; Vyazovskiy et al., 2011; Brown et al., 2012). Cortical columns are collections of highly interconnected neurons or neural assemblies that are thought to be a basic unit of the waking brain (Koch, 2004). During whole-animal sleep, most but not all the cortical columns are in a sleep-like state; and when an animal is awake, most but not all of the cortical columns are in a wake-like state (Rector et al., 2005). In turn, sleep intensity has been reported to be dependent on the number of columns in the sleep-like state during sleep, and in insomnia patients, it has been proposed that the perception of poor sleep quality (and perhaps NRS) is the result of having a higher than normal number of columns in the wake-like state during sleep (Krueger et al., 2008; Buysse et al., 2011). Importantly, the state of the cortical columns is homeostatically regulated: the probability of finding a column in a sleep-like state is dependent on the length of time it has spent in the wake-like state and vice-versa. Thus, while NRS may be the result of a higher than normal number of columns in the wake-like state during sleep; alertness and the speed and accuracy of performance may depend on the fraction of columns that are in the sleep-like state during wakefulness (Krueger et al., 2008). This is particularly relevant in the context of the ADHD-I subtype because it has been reported that ADHD-I subjects suffer from neurophysiological underarousal (Mayes et al., 2009), which in turn may lead to the experience of lethargy, sleepiness, or fatigue (Barkley et al., 1990; 1992; Goodyear & Hynd, 1992; Stanford & Hynd, 1994; Hartman et al., 2004; Calhoun & Mayes, 2005; Mayes et al., 2009). In the context of this discussion, neurophysiological underarousal in ADHD-I may be the result of a higher than normal number of columns in the sleep-like state during wakefulness, and fatigue may be the result of this neurophysiologic underarousal and, thus, part of the ADHD-I phenotype. In turn, given the homeostatic regulation of cortical column states, it would be expected that, as a result of underarousal during wakefulness, fewer
cortical columns would switch to the sleep-like state during sleep, effectively setting the conditions for NRS and resulting in the perception of poor sleep quality and high PSQI scores. In this regard, the ADHD-I phenotype may be described as the result of a perpetual cycle, where underarousal during wakefulness leads to NRS, and NRS leads to underarousal during wakefulness.

4.1.2.3 Gender x subtype interaction

While I found no gender differences on any sleep-related variables, MANCOVA revealed that a statistically significant ADHD subtype x gender interaction affects the perception of fatigue. This appears to apply to females in particular, since FSS scores were comparable in males of the Inattentive and Combined subtypes while, for females, FSS scores were markedly higher for Inattentive females than for Combined females.

While this is, to the best of my knowledge, the first study to report an ADHD-subtype x gender interaction on the perception of fatigue, it has previously been reported that gender is a significant factor in conditions that are highly associated with fatigue, such as Fibromyalgia Syndrome and Chronic Fatigue Syndrome (Jason et al., 1990; Wolfe, 1993). The high prevalence of fatigue in women is likely the result of complex interactions between female gonadal hormones and various aspects of human physiology, and it has been proposed to be related to reproductive correlates and biopsychosocial factors such as stress-associated immune modulation (Jason et al., 1990; Harlow et al., 1998; Glaser & Kiecolt-Glaser, 1998).

Interestingly, my results suggest that the ADHD subtype is an additional factor that contributes to the etiology of fatigue in women. Given that subjective fatigue in ADHD-C females was comparable to subjective fatigue in ADHD males of either subtype, the combination of being a female and being of the ADHD-I subtype appears to be a predisposing factor for high fatigue, and thus, female ADHD-I patients may be the ideal models for investigating the etiology and pathophysiology of fatigue. In this respect, my results highlight the need for more research focusing on the role of gender differences in the etiology of ADHD subtypes.
4.1.2.4 Conclusion

As evidenced by the finding that the majority of the subjects in this study reported sleepiness, fatigue, and poor sleep quality, the results discussed herein suggest that sleep disturbances pose a significant problem for adults with ADHD, making the management of sleep problems imperative as a prelude to the treatment of ADHD. Moreover, the results discussed in this section suggest that differences between ADHD subtypes are not limited to daytime function, but rather extend to the realm of sleep. As such, the data discussed in this section indicate that with regards to Hypothesis 1, subjective correlates of sleep differ in ADHD-I and ADHD-C groups; and, thus, the null hypothesis is rejected. I speculate that differences in the perception of sleep quality and fatigue; and differences in the interrelationships between sleep quality, sleepiness, and fatigue are manifestations of fundamental differences in the neurological make-up of the ADHD-I and ADHD-C subtypes.

4.2 Phase II

4.2.1 Chronotypes in ADHD

This segment of the study was conducted to test Hypothesis 2: In ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality, the circadian regulation of sleep-wake cycles differs in ADHD-I and ADHD-C groups. In the sections that follow, the results presented in section 3.2.1 are discussed.

4.2.1.1 Subjective correlates of circadian phase

Circadian preference or “morningness-eveningness” is a measure of inter-individual preferences in the timing of behaviours (Liu et al., 2000), where “evening persons” are reported to reach peak body temperatures and alertness approximately 2-3 h later than “morning persons” (Kerhof, 1985). The results presented in this section revealed that eveningness is a predominant feature in adults with ADHD – more so than in non-ADHD populations.

Demographic studies of chronotype distributions indicate that subjects with an intermediate chronotype predominate in young adults aged 18-30, while progression into middle age and late
adulthood coincides with a shift in chronotype towards morningness (Adan & Natale, 2002; Taillard et al., 2004; Lehnkering & Siegmund, 2007; Bahammam et al., 2011; Paine et al., 2006) (Table 4.2). Such was not the case in this study, as a large proportion of subjects between the ages of 18-30 reported evening preference (46% moderately evening, 31% definitely evening), and while age appeared to be associated with a shift toward earlier circadian preferences, the proportion of subjects with evening preference in the 31-60 age group was higher than in other studies (Table 4.2).

The predominance of eveningness in ADHD has previously been reported (Rybak et al., 2007). Particular to this study, it is important to point out that while the high count of subjects with evening preference was expected because all the subjects of this study had sleep-related complaints (specifically, excessive daytime sleepiness and/or poor sleep quality), even the larger sample (n = 126) from which the present study subjects were selected (see Materials and Methods - Recruitment Process) exhibited a disproportionate distribution towards an evening preference [subjects 18-30 years (n = 34): 3% moderately morning, 27% intermediate, 29% moderately evening, and 41% definitely evening; subjects 31-60 years (n = 91): 1% definitely morning, 21% moderately morning, 41% intermediate, 32% moderately evening, and 6% definitely evening], suggesting that the proportion of subjects with evening circadian preference is higher in ADHD regardless of the presence of sleep disturbances.

Put together (that is, combining moderately evening and definitely evening chronotype groups without stratifying subjects into age groups of 18-30 and 31-60 years), 14% of subjects in this study were morning types (AM), 34% were intermediate types (I), and 52% were evening types (PM) (Table 3.9). Mean age differed significantly in these chronotype groups, with the AM group being significantly older than the PM group – a finding that was well in line with reports on the phase advancing effects of age on circadian preference (Gander et al., 1993; Carrier et al., 1997). On the other hand, the distribution of subjects with morning, intermediate, and evening chronotypes was comparable in ADHD-I and ADHD-C groups, and in males and females, suggesting that evening circadian preference is a predominant feature of ADHD, regardless of ADHD subtype and/or gender.
Table 4.2 Comparison of chronotype distribution in the present study and five other reports

<table>
<thead>
<tr>
<th>Age range</th>
<th>Morning chronotype n (%)</th>
<th>Intermediate chronotype n (%)</th>
<th>Evening chronotype n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current study</td>
<td>18-30</td>
<td>0 (0%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td></td>
<td>31-60</td>
<td>8 (19%)</td>
<td>16 (37%)</td>
</tr>
<tr>
<td>Adan &amp; Natale (2002)</td>
<td>18-30</td>
<td>338 (16%)</td>
<td>1273 (60%)</td>
</tr>
<tr>
<td>Bahamman et al. (2011)</td>
<td>18-32</td>
<td>138 (18%)</td>
<td>417 (55%)</td>
</tr>
<tr>
<td>Taillard et al. (2004)</td>
<td>44-58</td>
<td>347 (62%)</td>
<td>207 (37%)</td>
</tr>
<tr>
<td>Paine et al. (2006)</td>
<td>30-49</td>
<td>1257 (50%)</td>
<td>1127 (45%)</td>
</tr>
<tr>
<td>Lehnkering &amp; Siegmund, (2007)</td>
<td>N/A</td>
<td>494 (18%)</td>
<td>1551 (58%)</td>
</tr>
</tbody>
</table>

4.2.1.2 Objective correlates of circadian phase

DLMO test results were used as objective correlates of circadian phase. For the subjects of this study, DLMO occurred at 21:40 ± 01:35 h. DLMO for the subjects of this study is delayed in relation to that reported for normal populations: Burgess & Fogg (2008) reported DLMO at 20:50 ± 01:12 h, and Rahman et al. (2009) reported DLMO at 20:35 ± 01:08 h in healthy subjects. Conversely, DLMO at 23:10 ± 02:18 h (Nagtegaal et al., 1998) and at 23:06 ± 01:43 h (Rahman et al., 2009) have been reported in DSPS, suggesting that the occurrence of DLMO at 23:00 or later is indicative of DSPS. The prevalence of DSPS in healthy populations has been reported to be between 0.13% and 0.7% (Schrader et al., 1993; Ando et al., 1995; Yazaki et al., 1999). In this study, DLMO occurred at 23:00 h or later in 23% of the subjects of this study, suggesting an alarmingly high prevalence of DSPS in ADHD. Altogether, the results presented in this section suggest a delayed circadian phase that is in line with the predominance of evening chronotypes in ADHD.

Of note, neither mean DLMO time nor the proportion of subjects with suspected DSPS (i.e. with DLMO at 23:00 or later) differed significantly in ADHD subtype groups. These findings, together with the results presented in the previous section (i.e. comparable MEQ and distribution of chronotypes across ADHD-I and ADHD-C groups) indicate that – in regards to Hypothesis 2a – correlates of circadian phase do not differ in ADHD-I and ADHD-C groups, and, thus, the null hypothesis cannot be rejected.
4.2.1.3 Associations between circadian preference, DLMO time, and the core symptoms of ADHD differ in ADHD-I and ADHD-C

To better understand whether and how circadian cycles affect the core symptoms of ADHD, I conducted a series of Pearson partial correlations which revealed that – with regards to Hypothesis 2b – the relationships between circadian preference, DLMO, and ADHD symptoms differ in ADHD subtypes: when data were stratified into ADHD-I and ADHD-C subtype groups, different sets of correlations were found between the two groups (Table 3.12). Thus, the null hypothesis is rejected. The results presented in section 3.2.1.4 are discussed in the sections that follow.

4.2.1.3.1 ADHD-I

In ADHD-I subjects, inattention scores correlated positively with DLMO, indicating that later chronotypes are associated with more severe deficits of inattention. Although a strong correlation between subjective eveningness and inattention has previously been reported (Rybak et al., 2007; Caci et al, 2009; Bae et al., 2010), my findings are unique in relation to these studies in that I found a correlation between inattention scores and a biological marker of circadian phase. In fact, had I examined relationships between inattention scores and subjective circadian preference only, statistical analyses would have yielded non-significant results because MEQ scores – from which the classification of circadian preference was obtained – did not correlate with DSM-IV-I T-scores. MEQ scores did not correlate with DLMO, either, a finding that in itself is interesting because it infers that subjective circadian preference is not in line with biological markers of circadian phase, which in turn would suggest that associated with the Inattentive subtype is a lack of awareness of the self with regards to endogenous processes related to circadian cycles.

A delayed DLMO is indicative of circadian phase shift delays (Burgess et al., 2002), and, in this respect, a significant proportion of study subjects may have met criteria for DSPS. DSPS is a circadian sleep disorder in which subjects suffer from a delay in the timing of circadian rhythms in relation to the 24 h cycle of the earth, such that onset of the biological day and the biological night are delayed in relation to the onset of the objective day and the objective night of the earth. In an attempt to conform to socially imposed schedules, subjects with phase shift delays often
go to bed earlier and wake up earlier than they would spontaneously (Mongrain et al., 2004) and this, in turn, leads to sleep disturbances as well as excessive daytime sleepiness (Zee et al., 2013). It may be inferred from this that some of the subjects with delayed DLMO in this study suffered from sleep disturbances and excessive daytime sleepiness, and since sleep disturbances and sleepiness are associated with deficits in daytime function (Gross et al., 1999; Van Dongen et al., 2003), the finding that delayed DLMO correlated positively with inattention scores in ADHD-I subjects was not surprising.

The correlation between DLMO and inattention also makes sense when sleep inertia is taken into consideration. Sleep inertia is defined as the period of time immediately following awakening during which alertness and performance are significantly impaired (Balkin & Badia, 1988; Silva & Duffy, 2008). Although the effects of sleep inertia on cognitive performance rarely exceed 30 min (Tassi & Muzet, 2000), sleep inertia can last anywhere from 1 min to 4 hrs (Webb & Agnew, 1964; Jewett et al., 1999; Scheer et al., 2008), and there is evidence to suggest that the duration and intensity of sleep inertia are affected by circadian cycles, as waking during the biological night – which is bound to happen in subjects with a delayed circadian phase attempting to conform to socially imposed schedules – has been reported to be associated with longer and more severe effects of sleep inertia (Rodgers et al., 2006; Silva & Duffy, 2008; Scheer et al., 2008). Thus, the positive correlation found between DLMO times and inattention scores may have been mediated in part by mechanisms involved with sleep inertia and the time of day.

Sleep inertia may be of particular relevance to the pathology of ADHD-I. The switch from sleep to wakefulness is not an immediate process but, rather, it is a transitional process that takes time to complete (Ferrara & De Gennaro, 2000; Silva & Duffy, 2008), and sleep inertia has been conjectured to be a continuation of a sleepy state, characterized by a lowered level of arousal and a more synchronized EEG than during the usual wake state (Malmo, 1959; Tassi & Muzet, 2000). Importantly, intensity of sleep and wakefulness is related to the ratio of cortical columns in the sleep-like and wake-like states (Rector et al., 2005; Krueger et al., 2008; Buysse et al., 2011) and, thus, it would be expected that the duration and intensity of sleep inertia be related to the rate at which cortical columns switch from the sleep to wake states. This is important because, as proposed in section 4.1.2.2.2, poor sleep quality in ADHD-I may be the result of a lower than normal number of cortical columns in the sleep-like state and, given that the state of
cortical columns is homeostatically regulated (Krueger et al., 2008; Buysse et al., 2011), the transition from sleep to wakefulness may be slower in ADHD-I and, thus, the duration and effects of sleep inertia may be more pronounced in these subjects. In this respect, I propose that while sleep inertia is a universal phenomenon, the neurobiology of ADHD-I may be associated with more profound effects of sleep inertia that, importantly, have a significant effect on the regulation of attention in ADHD-I.

4.2.1.3.2 ADHD-C

4.2.1.3.2.1 Inattention

Contrary to what was observed in ADHD-I, the partial correlations conducted in the ADHD-C group revealed no significant associations between inattention scores and DLMO or MEQ, suggesting that circadian cycles are not involved in the pathology of inattention in ADHD-C. The finding was surprising because the deleterious effects of delayed circadian phases on daytime function have been reported (Rybak et al., 2007; Caci et al., 2009; Bae et al., 2010) and, thus, it was expected that, as was the case in ADHD-I, delays in DLMO would be associated with increases in the severity of inattentive symptoms. The finding is interesting, not only because it suggests ADHD subtype differences with regards to the neurological mechanisms underlying inattention, but also because it implies that, at least when it comes to attention, ADHD-C subjects are immune to the deleterious effects of delayed circadian phase on daytime function.

Why delays in circadian phase are associated with more severe inattention in ADHD-I but not in ADHD-C cannot be determined based on the data collected in this study. However, I speculate that sleep inertia is an important factor in the association between attention and circadian phase. There are several factors that contribute to the intensity and duration of sleep inertia, including prior sleep deprivation, prior sleep duration, sleep stage prior to awakening, and circadian cycles (Tassi & Muzet, 2000; Silva & Duffy, 2008). Importantly, the association between circadian cycles and sleep inertia is not one-dimensional but, rather, there is an interaction between the two factors. In a study designed to investigate the circadian regulation of cognitive performance during sleep inertia, Scheer et al. (2008) compared cognitive performance across different circadian time points in three situations that differed in the degree of sleep inertia intensity:
immediately upon awakening from stage 2 sleep – a situation representative of high sleep inertia; 20 minutes after awakening – a situation representative of intermediate sleep inertia; and during prolonged wakefulness – a situation representative of low sleep inertia. The study revealed that circadian variation in cognitive performance was highest when subjects were tested immediately upon awakening, and lowest when subjects were tested during prolonged wakefulness and, thus, Scheer et al. (2008) concluded that circadian regulation of cognitive performance is strong when sleep inertia is high and relatively weak when sleep inertia is dissipated. This is important because, as discussed in sections 4.1.2.2.2 and 4.2.1.3.1, the neurobiology of ADHD-I – specifically, neurobehavioural underarousal and NRS – may set the conditions for more profound and longer effects of sleep inertia and, in this respect, higher sleep inertia may lead to stronger circadian modulation of cognitive performance and, thus, give rise to significant associations between DLMO time and inattention scores in ADHD-I. Of note, sleep inertia is hypothesized to be a continuation of a sleepy state that is associated with reduced cerebral metabolism (Dinges, 1990; Tassi & Muzet, 2000) and, in line with this, it has been proposed that any factors likely to increase neuronal activity or cerebral metabolism may reduce the effects of sleep inertia (Tassi & Muzet, 2000). Given that higher neurological activity has been proposed in ADHD-C (Mayes et al., 2009), then, it is possible that the effects of sleep inertia are weaker and shorter in ADHD-C and, in view of the findings of Scheer et al. (2008) that circadian regulation of cognitive performance is weak when sleep inertia is dissipated, it is possible that the lack of association between DLMO time and inattention scores in ADHD-C is a reflection of weak circadian regulation of cognitive performance that stems from low sleep inertia in ADHD-C.

4.2.1.3.2.2 Hyperactivity and Impulsivity

Another interesting – and rather puzzling – finding in the Combined subtypes was that DSM-IV-TR-H/I T-scores correlated negatively with DLMO (and positively with MEQ), suggesting that delays in the timing of DLMO (and subjective circadian preference) are associated with attenuation of hyperactive/impulsive symptoms in ADHD-C.

I had anticipated that ADHD subjects with delayed DLMO would have more severe problems with hyperactivity/impulsivity, not only because sleep disturbances have been reported to be
associated with the symptoms of ADHD (as discussed in section 1.4.1), but also because in children with ADHD, it has been postulated that hyperactivity is a coping mechanism to counteract the effects of daytime sleepiness associated with sleep disturbances (Bartholomew & Owens, 2006; Goll & Shapiro, 2006). Contrary to these expectations, I found delays in DLMO to be associated with attenuation of hyperactivity and impulsivity. The association does not appear to be mediated by fatigue (one may suspect that delayed DLMO results in a tired subject whose fatigue dampens the subject’s hyperactivity), as the addition of FSS scores to the analyses did not lead to any significant correlations between FSS and DLMO times or ADHD symptoms severity (data not shown).

Although counterintuitive at first, the findings make sense if one takes into consideration that a delayed DLMO is indicative of a delayed circadian phase, and that a delayed circadian phase, in turn suggests a delayed dim light melatonin offset (DLMOff). In this respect, it is possible that subjects with delayed DLMO may have been affected by the presence of melatonin during wake times as a result of delayed DLMOff. In line with this, it has been reported that – other than timing – the duration and pattern of melatonin secretion in subjects with DSPS is comparable to that of healthy subjects (Shibui et al., 1999) and, moreover, it has been postulated that one of the mechanisms underlying DSPS is decreased response to the phase-advancing effects of light (Kolla & Auger, 2011; Zee et al., 2013), supporting the idea that delayed DLMO is also associated with delayed DLMOff.

The significance of delayed DLMOff is that in subjects attempting to conform to socially acceptable schedules, earlier than ideal wake times may lead to being awake during the biological night when melatonin secretion is still relatively high. Within the context of ADHD, the secretion of melatonin during waking hours is especially important because of the antagonistic relationship that exists between dopamine and melatonin signaling: in the retina, melatonin is a potent inhibitor of DA and vice-versa (Dubocovich, 1983; Tosini & Dirden, 2000; Jaliffa et al., 2000; Khaldy et al., 2002) and in rat hypothami, physiological concentrations of melatonin have been reported to inhibit the stimulated release of dopamine (Zisapel, 2002).

Dopaminergic signaling in the striatum also appears to be highly regulated by melatonin (Alexiuk & Vriend, 2007): in rats, peaks in melatonin coincide with nadirs in DA (Khaldy et al.,
2002), and melatonin administration has been reported to lead to decreases in DA firing in the striatum (Castillo Romero et al., 1992; Hamdi, 1998), as well as inhibition of locomotor activity (Hamdi, 1998). The antagonistic effects of melatonin on dopamine signaling in the striatum appear to be mediated by the D<sub>2</sub> receptor, as melatonin has been reported to increase the affinity of D<sub>2</sub> receptors for DA (Hamdi, 1998). Since DA release in the striatum is inhibited by presynaptic D<sub>2</sub> autoreceptors (Kalivas, 1993; Hamdi, 1998), it is postulated that increased affinity of D<sub>2</sub> autoreceptors to DA by melatonin would augment the inhibitory effect of these receptors on DA release and, thus, reduce locomotor activity in rats (Hamdi, 1998). This is important because, as discussed in section 1.2.2.3.3, hyperactivity/impulsivity in ADHD is postulated to arise from overactivity in the striatum due to low tonic/high phasic DA secretion (Castellanos, 1997), and the attenuating effects of stimulant medications on hyperactivity/impulsivity are thought to be mediated through activation of D<sub>2</sub> autoreceptors and subsequent attenuation of phasic DA bursts in the striatum (Seeman & Madras, 1998; Solanto, 2002). Altogether, this would imply that – like ADHD stimulant medications – melatonin has an attenuating effect on hyperactivity/impulsivity and, thus, delayed DLMOff would have a potentially protective effect in subjects with ADHD-C.

4.2.1.4 Conclusion

The results discussed in this section indicate that the evening chronotype is predominant in adults with ADHD, suggesting that abnormalities in the regulation of circadian cycles are partly accountable for the sleep disturbances of ADHD. Importantly, the results indicate that almost half of subjects with evening chronotypes (moderate + definite) have clinically relevant delays in the onset of melatonin secretion, suggesting a high risk for DSPS in these subjects. Of interest, I identified ADHD subtype differences in the associations between circadian preference, DLMO, and severity of the core symptoms of ADHD. In ADHD-I subjects, inattention but not hyperactivity/impulsivity correlated strongly with DLMO time; while in ADHD-C subjects, hyperactivity/impulsivity but not inattention correlated strongly (and negatively) with DLMO time, suggesting that the etiological factors contributing to the core symptoms of inattention and hyperactivity/impulsivity differ in ADHD subtypes. At the clinical level, these findings support, not only the notion that circadian cycles affect the core symptoms
of ADHD, but also that how circadian cycles affect the core symptoms of ADHD differs between ADHD subtypes, thus highlighting the importance of distinguishing Inattentive from Combined subtypes, as well as screening for sleep disorders in clinical settings.

This study is, to the best of my knowledge, the first to identify significant associations between a biological marker of circadian phase and the core symptoms of ADHD. The perplexity of some of the results discussed herein, namely the lack of association between subjective and objective measures of circadian phase in ADHD-I, and the negative correlation between DLMO time and the severity of hyperactivity/impulsivity in ADHD-C subjects merits further research in the area to identify the factors accounting for these findings.

4.2.2 Objective assessment of sleep

4.2.2.1 Macrostructure of sleep in ADHD

As far as techniques for the objective assessment of sleep go, PSG is among the most important tools and, currently, it is considered the gold standard in the diagnosis of sleep disorders (Bloch, 1997; Kushida et al., 2005). Nevertheless, objective studies of sleep in adult ADHD are lacking and, to the best of my knowledge, only two PSG studies (Philipsen et al., 2005; Sobanski et al., 2008a) of sleep in adult ADHD have been published to date.

For this portion of the study, sleep in adults with ADHD was assessed by PSG over the course of two nights. Without stratifying the data into ADHD-I and ADHD-C groups, the number of awakenings, as well as percentages of stage 1, stage 2, SWS, and REM sleep were comparable between the first and second nights of PSG recordings; and while subjects appeared to have increased TST and SE, and decreased SOL and REML on the second night, repeated-measures MANCOVA revealed no significant differences on any measures of PSG between the first and second nights of recordings, suggesting that the macrostructure of sleep in my study subjects was not affected by first-night effects (Table 4.3). This was not in line with the findings of Philipsen et al. (2005), who reported significant first-night effects on measures of total sleep time, sleep efficiency, and arousals. There are, to the best of my knowledge, no other published studies on first-night effects in adults with ADHD.
Because the current study was designed to compare sleep in the Inattentive and Combined subtypes of ADHD, normative PSG data from age- and gender-matched healthy controls were not collected. Thus, it is difficult to draw any conclusions as to how sleep in adults with ADHD compares to sleep in healthy controls. Depending on a variety of factors – including genetics, age, and prior sleep history, among others – sleep duration can vary from approximately 6.5 hrs to 9 hrs (Hirshkowitz et al., 1992; Bonnet & Arand, 1995). In the Principles and Practices of Sleep Medicine, Carskadon and Dement (1989) report that normal sleep is composed of 2-5% stage 1, 45-55% stage 2, 13-23% SWS, and 20-25% REM sleep. More recently, Ohayon et al. (2004) conducted a meta-analysis on the effects of age on sleep parameters and reported normative PSG values in different age groups. According to these analyses, there are age-related decreases in TST (approximately 10 minutes per decade), SE (approximately 3% per decade), SWS percentage (approximately 2% per decade), REM sleep percentage, and REM sleep latency; and age-related increases in SOL and the percentages of stage 1 and stage 2 sleep (Ohayon et al., 2004). Given that the mean age of my study group was 38 ± 10 years (39 ± 12 years for ADHD-I and 37 ± 9 for ADHD-C), approximate values for PSG parameters of sleep at age 40 were obtained from the study by Ohayon et al. (2004). These values, along with normative data provided by Carskadon & Dement (1989) are listed in Table 4.3.
Table 4.3 Normative polysomnography values

<table>
<thead>
<tr>
<th></th>
<th>Current study</th>
<th>Caruskadon &amp; Dement, 1989</th>
<th>Ohayon et al., 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First Night</td>
<td>Second Night</td>
<td></td>
</tr>
<tr>
<td>TST mean ± SD (minutes)</td>
<td>356.6 ± 73.0</td>
<td>408.4 ± 81.1</td>
<td>N/A</td>
</tr>
<tr>
<td>SE mean ± SD (percentage)</td>
<td>77.6 ± 15.8</td>
<td>84.3 ± 12.2</td>
<td>N/A</td>
</tr>
<tr>
<td>SOL mean ± SD (minutes)</td>
<td>39.2 ± 48.5</td>
<td>20.6 ± 27.7</td>
<td>N/A</td>
</tr>
<tr>
<td>REM L mean ± SD (minutes)</td>
<td>101 ± 63</td>
<td>90 ± 52</td>
<td>N/A</td>
</tr>
<tr>
<td>Awakenings mean ± SD</td>
<td>18 ± 10</td>
<td>18 ± 13</td>
<td>N/A</td>
</tr>
<tr>
<td>Percentage of TST mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>6.4 ± 4.7</td>
<td>5.9 ± 3.3</td>
<td>2-5%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>53.9 ± 7.7</td>
<td>53.9 ± 9.5</td>
<td>45-55%</td>
</tr>
<tr>
<td>SWS</td>
<td>18.8 ± 8.1</td>
<td>17.9 ± 7.8</td>
<td>13-23%</td>
</tr>
<tr>
<td>REM</td>
<td>20.8 ± 6.4</td>
<td>22.3 ± 6.8</td>
<td>20-25%</td>
</tr>
</tbody>
</table>

N/A= not available

Following the norms listed in Table 4.3 it appears that, as a whole, the subjects of this study had decreased TST and SE, and increased SOL and REML on both the first and second nights of PSG recordings. Admittedly, the comparison of sleep in the subjects of this study to normative values of an independently published study is not ideal, and the concomitant collection of PSG data from age- and gender-matched healthy controls would have been advantageous in establishing more conclusive evidence on how sleep in the adult with ADHD deviates from healthy sleep. Nevertheless, the findings of this study are partially in agreement with the work of Sobanski et al. (2008a) who reported that adults with ADHD (n = 34) exhibited elevated SOL, awakenings and stage 1 sleep percentage; as well as reduced SE and REM sleep percentage in comparison to healthy controls. It should be noted that while that group characteristics in the current study and that of Sobanski et al. (2008a) were relatively comparable in terms of gender ratios and axis-I co-morbidities; in the study by Sobanski et al
(2008a), the ADHD group (as well as the age-matched control group) was slightly younger (36 ± 9 years) and the proportion of ADHD-I and ADHD-C subjects (18% ADHD-I, 82% ADHD-C) differed vis-a-vis the present study. These study group differences as well as other possible unaccounted-for factors such as ADHD symptom severity and differences in PSG laboratory techniques may have contributed to the differences in the nature of the findings in this study and that of Sobanski et al. (2008a). Indeed, factors such as age, gender, sample size, and environmental conditions (e.g. noise, light) can affect the macrostructure of sleep (Terzano & Parrino, 2000, Ohayon et al., 2004) and give rise to a different set of PSG results – a fact that is evident in the study by Philipsen and colleagues (2005), in which PSG assessment of sleep in an ADHD group with a smaller sample size (n=20), lower mean age (33 ± 10 years of age), a different proportion of males to females (45% females), and a different proportion of ADHD subtypes (all subjects were ADHD-C) yielded no significant differences when sleep was compared to age- and gender-matched healthy controls.

4.2.2.1.1 Indices of sleep disordered breathing and periodic limb movements in sleep

There is evidence in the literature to suggest that the prevalence of PLMS (Picchietti et al., 1998; 1999; Konofal et al., 2001; Golan et al., 2004; Sadeh et al., 2006; Oner et al., 2007; Cortese et al., 2009) and SDB (Chervin et al., 1997; Golan et al., 2004; Huang et al., 2004; Gau et al., 2007) in children diagnosed with ADHD is higher than that in healthy controls. Whether the same applies to adult ADHD is not clear, given that there is only one report of increased PLMI (Philipsen et al., 2005), one report of increased frequency of RLS (Zak et al., 2009) and no reports of SDB in adults diagnosed with ADHD. To address this issue, indices of sleep-disordered breathing and periodic limb movements were evaluated in this study.

4.2.2.1.1.1 ADHD appears to be associated with periodic limb movements in sleep

For the subjects of this study, mean PLMI values in TST were within a range associated with mild PLMS (PLMI between 5 and 25), albeit with very high variability as indicated by the large standard deviations (Table 3.13). After stratification of study subjects according to PLMI values, a total of 36.8% of subjects met the criterion of PLMI ≥ 5 for diagnosis of PLMS (Table
3.14). This value is higher than that reported for normal populations: Bixler et al. (1982) reported that the prevalence of PLMS in healthy subjects between the ages of 30 and 45 years is 5-6%, and in a more recent study, Scofield et al. (2008) reported that the overall prevalence of PLMI > 15 in the general population is 7.6% (as opposed to 20.6% in this study). Thus, in line with the reports of Philipsen et al. (2005) and Zak et al. (2009), the findings of this study suggest an association between adult ADHD and PLMS.

4.2.2.1.1.2 ADHD appears to be associated with sleep-disordered breathing

To investigate the prevalence of SDB, study subjects were organized into groups according to AHI values in TST. Stratification revealed that AHI values were normal (<5) for 77.9%, mildly elevated (5 to 15) for 11.8%, moderately elevated (15 to 30) for 7.4%, and highly elevated (>30) for 2.9% of subjects; i.e. a total of 22.1% of subjects met the criterion of AHI ≥ 5 for diagnosis of SDB (Table 3.14). It is difficult to determine how these values compare to AHI in healthy populations, as the prevalence of SDB is significantly affected by a number of factors, including but not limited to body mass index (BMI), neck circumference, cholesterol levels, smoking, upper airway or facial abnormalities, and endocrine and/or metabolic disorders (Young et al., 2004). Gender also contributes to variability in the occurrence of SDB: the prevalence of SDB in adulthood is higher in males than in females, and in adults between the ages of 30 and 60, AHI ≥ 5 has been reported to occur in 9% of women and 24% of men (Young et al., 1993). Interestingly, the association between SDB and gender is age-dependent, as differences in the occurrence of SDB in men and women diminish with age. As such, Young and colleagues (1993) demonstrated that while the prevalence of SDB increases with each 10-year age increase, the rate of the increase in prevalence of SDB is higher for females, particularly in females advancing from their 40s to their 50s. Additionally, Tishler and colleagues (2003) reported that the odds ratio for increased AHI per decade is 2.41 in females and 1.15 in males.

Gender-related differences in the prevalence of SDB were observed in this study, as a higher proportion of males than females had AHI ≥ 5 (Table 4.4). The reported effects of age on SDB rates, however, were not seen in this study: only one out of 5 females in their 30s (20%) had AHI ≥ 5; and in females in their 40s and 50s, AHI values were in the normal range. The observed deviations in AHI frequency distribution in the females of this study across age
categories are likely to stem largely from small sample size, as only 17 females (3 in their 20s, 5 in their 30s, 6 in their 40s, and 3 in their 50s) were recruited to the study.

Table 4.4 Prevalence of SBD across age groups

<table>
<thead>
<tr>
<th></th>
<th>Current Study</th>
<th>Young et al., 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>n = 17</td>
<td>n = 51</td>
</tr>
<tr>
<td>20s</td>
<td>33.3%</td>
<td>0%</td>
</tr>
<tr>
<td>30s</td>
<td>20%</td>
<td>17.7%</td>
</tr>
<tr>
<td>40s</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>50s</td>
<td>0%</td>
<td>33.4%</td>
</tr>
<tr>
<td>Total</td>
<td>11.8%</td>
<td>25.4%</td>
</tr>
</tbody>
</table>

AHI frequency distribution across age groups also deviated from normative in the males of this study (Table 4.4). Contrary to the pattern of linear increases in the prevalence of SDB across age described by Young et al. (1993), prevalence rates of SDB followed an inverted U-shape pattern across age, and while prevalence of SDB in males in their 30s and 50s were comparable to normative data, the proportion of ADHD males aged 40-49 with AHI ≥ 5 was double that of healthy subjects in the study by Young et al. (1993), suggesting an association between SDB and ADHD in males in their 40s. It should be noted, however, that while the finding suggests an age-dependent association between SDB and adult ADHD, it is also possible that the elevated prevalence of SDB observed in the males of this study aged 40-49 may be an artifact stemming from confounding effects exerted by factors such as BMI, neck circumference, or smoking – which were not controlled for in this study; and possibly the smaller sample in comparison to the study by Young et al. (1993).

4.2.2.1.2 Indices of arousal

Arousals from sleep are transient elevations in vigilance levels caused by arousal stimuli or spontaneous vigilance level oscillations (Bonnet et al., 2007). Conventionally, arousals denote cortical activation (Halasz et al., 2004) and, as such, the American Sleep Disorders Association defines arousals as abrupt shifts in EEG frequency to theta, alpha, beta, and/or frequencies
higher than 16 Hz, but not spindles, which last at least 3 seconds in NREM sleep, and which are accompanied by concurrent increases in submental EMG amplitude in REM sleep (Bonnet et al., 2007).

Several factors affect the occurrence of EEG arousals. Some of these factors include previous sleep, as sleep deprivation leads to a reduction of EEG arousals on the following night of sleep (De Gennaro et al., 2001); age, as indices of arousal (AI) in NREM sleep are significantly higher in the elderly compared to adolescents, young adults, and middle aged adults (Boselli et al., 1998); and stage of sleep, as AI tends to be highest during stage 1 sleep, intermediate during stage 2 and REM sleep, and lowest during SWS (De Gennaro et al., 2001). Additionally, large inter-individual differences in the occurrence of EEG arousals have been reported (Muzet, 2005).

The fact that so many factors can impact on the occurrence of arousals is reflected in the high degree of variability in normative AI values reported by different studies. As shown in Table 4.5, normal AI values increase with age (Boselli et al., 1998; Bonnet & Arand, 2007), and in healthy subjects with a mean age of 35 years, AI can range from 13.7 to 21 (Mathur & Douglas, 1995; Bonnet & Arand, 1996). Despite this high variability, indices of arousal in NREM, REM, and TST were elevated for the subjects of this study in relation to normative values (Table 4.5), suggesting that sleep in ADHD is associated with a comparatively higher frequency of arousals.

### Table 4.5 Normative indices of arousal

<table>
<thead>
<tr>
<th></th>
<th>Mean AI for current study</th>
<th>Normative AI</th>
<th>Age</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>20.2 ± 11.3</td>
<td>21</td>
<td>35 ± 2 SE</td>
<td>Mathur and Douglas, 1995</td>
<td></td>
</tr>
<tr>
<td>18.6 ± 11.7</td>
<td>14.7 ± 2.6</td>
<td>36 ± 8</td>
<td>Bonnet and Arand, 1996</td>
<td></td>
</tr>
<tr>
<td>22.0 ± 10.9</td>
<td>17.8 ± 2</td>
<td>20-39</td>
<td>Boselli et al., 1998</td>
<td></td>
</tr>
<tr>
<td>16.7 ± 10.1</td>
<td>10.8 ± 4.6</td>
<td>40-59</td>
<td>Bonnet and Arand, 2007</td>
<td></td>
</tr>
<tr>
<td>19.9 ± 12.6</td>
<td>16.8 ± 6.2</td>
<td>30s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.8 ± 12.1</td>
<td>16.5 ± 5.6</td>
<td>40s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.5 ± 7.8</td>
<td>21.9 ± 8.9</td>
<td>50s</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NREM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.7 ± 12.4</td>
<td>14.8 ± 3.5</td>
<td>20-39</td>
<td>Boselli et al., 1998</td>
<td></td>
</tr>
<tr>
<td>22.8 ± 11.9</td>
<td>18.2 ± 4.2</td>
<td>40-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>REM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.7 ± 13.0</td>
<td>13.3 ± 3.4</td>
<td>20-39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.3 ± 15.5</td>
<td>14.7 ± 6.4</td>
<td>40-59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Breakdown of total AI values into PLMA, AHA, RERA, and spontaneous arousals revealed that the latter made up the bulk of total arousals in TST (Table 3.13). This was not entirely surprising given that spontaneous arousals – that is, arousals that occur without any evident sources of stimuli (Chen et al., 2011) – are natural components of sleep (Carskadon et al., 1982; Boselli et al., 1998; Halasz et al., 2004). While the exact role and mechanisms underlying spontaneous arousals in sleep are not well understood, cumulative evidence from studies on the microstructure of sleep suggest that the occurrence of a certain amount of arousals is essential for maintaining the intrinsic organization of sleep (Halasz et al., 2004).

4.2.2.2 There are no ADHD subtype differences in objective measures of sleep

PSG measures were compared in ADHD-I and ADHD-C subjects across the first and second nights of recordings with a repeated measures MANCOVA to test Hypothesis 3: In ADHD adults with complaints of excessive daytime sleepiness and/or poor sleep quality, objective measures of sleep differ in ADHD-I and ADHD-C groups.

Regarding Hypothesis 3a, the analysis revealed no significant differences in PSG variables of sleep macrostructure between ADHD groups or between the first and second nights of recordings and, thus, the null hypothesis cannot be rejected (Table 3.13). Moreover, with regards to Hypotheses 3b and 3c, the occurrence of respiratory and periodic limb movement events, as well as indices of arousal were comparable in ADHD subtypes (Table 3.13); and the distribution of subjects with normal, mildly elevated, moderately elevated, and highly elevated AHI and PLMI values did not differ significantly between ADHD-I and ADHD-C groups (Table 3.14). Thus, the null hypotheses could not be rejected. Altogether, these findings suggest, not only that sleep is comparable in ADHD-I and ADHD-C subjects, but also that ADHD subjects are not affected by first-night effects.

The finding that PSG measures of sleep were comparable between ADHD-I and ADHD-C was somewhat surprising because significant ADHD subtype differences in sleep have previously been reported, albeit not in adults. In this respect, studies of children with ADHD have indicated greater daytime sleepiness but no sleep problems in children with ADHD-I (Lecendreaux et al., 2000; LeBourgeois et al., 2004); while sleep in children with ADHD-C has been reported to be
associated with more frequent reports of problems such as trouble falling asleep, involuntary movements, restlessness, and awakenings (Corkum et al., 1999; Mayes et al., 2009), as well as decreased sleep efficiency and more fragmented sleep as measured by PSG (Ramos-Platon et al., 1990). Put together, the findings reported in these studies suggest that sleep may constitute another dimension in which ADHD subtypes differ and, based on the nature of the sleep problems associated with each subtype, it has been proposed that ADHD-I is associated with physiologic underarousal, while in ADHD-C, the persistence of problems with hyperactivity in wakefulness as well as in sleep may render ADHD-C a “24 hr disorder” (Cortese et al., 2006; Mayes et al., 2009).

The results presented in section 3.2.2 provide no evidence to suggest that ADHD subtype differences extend to the realm of sleep in adults with ADHD. However, whether the lack of significant differences in PSG measures of sleep in ADHD subtypes is a true reflection of sleep in ADHD-I and ADHD-C, or merely a false-negative result is not clear.

If the results are valid and sleep is, indeed, comparable in ADHD subtypes, how can these results be reconciled to reports of ADHD subtype differences in the sleep of children with ADHD? Given that sleep was reported as comparable in children with ADHD-I and healthy controls, while sleep in ADHD-C was associated with more problems (Corkum et al., 1999; Lecendreaux et al., 2000; LeBourgeois et al., 2004; Mayes et al., 2009), it is possible that differences in the occurrence of sleep problems in ADHD-I and ADHD-C diminish with age, such that sleep becomes comparable between subtypes by the time subjects reach adulthood, either by the development and increase in the frequency of sleep problems in children with ADHD-I as they progress into adulthood, or by attenuation of sleep problems in children with ADHD-C as they progress into adulthood. The latter is a less likely possibility given that PSG measures of sleep in the ADHD subjects of this study indicate sleep abnormalities in the forms of decreased TST and SE, and increased SOL and REM L, as discussed in section 4.2.2.1.

On the other hand, it is possible that significant differences in PSG measures of sleep between ADHD-I and ADHD-C may have been missed, giving rise to false negative results. For the repeated measures MANCOVA conducted on the PSG data of this study, the observed statistical power associated with the test of between-subjects effects was 0.787 and, accordingly, the probability of type II error – that is, erroneously assuming no ADHD subtype differences in
PSG measures of sleep – was 0.213. Several factors can contribute to type II errors, including small total sample size, unequal sample sizes in groups of comparison, low statistical power, and small effect sizes (Berry et al., 1998). These parameters are closely interrelated, and Berry and colleagues (1998) established functional equations relating total sample size to effect size for various values of sample size ratios and statistical power. Intra-polation into these functional equations revealed that for the parameters of this study (i.e. sample size of 68, ADHD-I to ADHD-C ratio of 2:3, and statistical power set at 0.80), only medium to large effect sized differences could reach statistical significance, suggesting that ADHD subtype differences of a smaller magnitude may have gone undetected. Raising total sample size allows for the detection of weaker correlations and, thus, the addition of more subjects to this study may have uncovered significant ADHD subtype differences in PSG measures of sleep.

Non-significance may also have stemmed from failure to control for confounding factors masking ADHD subtype differences in PSG measures of sleep. Significant effects of mental and physical illness, as well as drug and alcohol use on the structure of sleep have been reported (Terzano & Parrino, 2000; Ohayon et al., 2004), and while subjects identified to have chronic or current Axis-I co-morbidities during the screening phase were excluded from this study, it is possible that certain co-morbidities may have gone undetected for some subjects of the study (due to judgment errors during the screening process or sub-syndromal co-morbidities), or that some subjects may have developed co-morbid Axis-I disorder(s) sometime between the date of recruitment to the study and the dates on which PSG data were collected.

Beyond the parameters of PSG, it is also possible that sleep in ADHD subtypes may differ in ways that cannot be detected within the framework of PSG or the macrostructure of sleep. In this regard, assessment of the microstructure of sleep may have been useful in the detection of ADHD subtype differences.

Microstructure of sleep refers to transient EEG phenomena or “phasic events” that manifest against the background EEG activity (Terzano & Parrino 2000). In relation to the macrostructure of sleep, which provides information on the temporal organization of sleep stages based on averaged EEG frequencies in 20-30 second epochs, assessment of phasic events allows for a deeper understanding of the dynamic processes underlying sleep. In particular, studies on the microstructure of sleep indicate that the ASDA definition of arousals may be an
oversimplification, and that arousals may be better understood as a continuum (Halasz et al., 2004). The microstructure of sleep includes arousal-related phasic events which do not follow the classic shift to low-amplitude high-frequency EEG but which, nevertheless, are associated with autonomic activation, albeit to a lower degree (Halasz et al., 2004). As such, arousals vary in strength, length and amplitude, ranging from high-amplitude low-frequency events such as delta bursts and K-complex sequences, to low-amplitude high-frequency events associated with the classic definition of EEG arousals (Terzano & Parrino, 2000; Halasz et al., 2004). An interesting aspect of the microstructure of sleep is that arousal-related phasic events appear to follow a cyclic pattern, alternating between a “Phase A”, consisting of phasic events, and a “Phase B”, which represent the intervals of background theta-delta activity (Terzano et al., 1985). Together, phases A and B constitute a cyclic alternating pattern (CAP), defined as “…periodic EEG activity (…) characterized by transient electrocortical events that are distinct from background EEG activity and (which) recur at up to 1 minute intervals” (Terzano et al., 2002).

An exciting aspect of CAP is that it serves to measure parameters of sleep stability that could not be detected by traditional methods (Halasz et al., 2004). A prime example of this is in the study of insomnia: whereas differences in the macrostructure of sleep in normal sleepers and insomnia patients had been difficult to detect, studies have shown significant correlations between CAP rates (the ratio of CAP time to sleep time) and subjective measures of sleep quality in insomnia patients (Terzano & Parrino, 1992; Paiva et al., 1993). Of relevance to this discussion, CAP rates have also been examined in ADHD, albeit not extensively and only in children. To date, there are only two published studies on CAP rates in children with ADHD, with one study reporting lower CAP rates during stage 2 sleep in children with ADHD than in healthy controls (Miano et al., 2006), and one study reporting no differences between children with ADHD and healthy controls (Prihodova et al., 2012). Notwithstanding the discordance in the nature of the results – which may well be related to the heterogeneity of ADHD – the examination of CAP rates in ADHD constitutes a new and exciting avenue of investigation to better understand sleep in ADHD.
4.2.2.3  **Associations between objective measures of sleep and the core symptoms of ADHD differ in the Inattentive and Combined subtypes of ADHD**

Pearson partial correlation analyses were conducted to determine whether there is a link between sleep and differences in the severity of the core symptoms of ADHD in ADHD subtypes. Regarding Hypothesis 3d, analyses revealed that ADHD-I and ADHD-C groups differ with regards to associations between objective measures of sleep and the core symptoms of ADHD, and, thus, the null hypothesis is rejected.

4.2.2.3.1  **RERA appears to be important in the pathology of inattention in ADHD-I**

Sleep in subjects with ADHD-I did not appear to be substantially associated with any symptoms of ADHD, and only one correlation – that of RERA and the CAARS subscale of Inattention/Memory Problems – was found to be statistically significant in the ADHD-I group. The finding is in line with previous studies reporting that sleep instability is associated with symptoms of inattention (see Section 1.4.1). However, it is difficult to ascertain why RERA, and not any other measures of arousal or sleep instability, correlated with Inattention/Memory problems in ADHD-I. While one may speculate that respiratory disturbances are important in the pathology of inattention in ADHD-I, evidence supporting this speculation is insufficient, given that neither AHI nor AHA correlated with the CAARS subscale of Inattention/Memory Problems in ADHD-I. Thus, further research on the nature of the associations between sleep and the core symptoms of ADHD in ADHD-I subtypes is needed before any significant conclusions can be made.

4.2.2.3.2  **REM sleep appears to be important in the pathology of ADHD-C**

Awakenings appear to be of importance to the phenotype of ADHD-C. This is evidenced by the finding that two of the characteristic symptoms of ADHD-C – that is, Hyperactivity/Restlessness and Impulsivity/Emotional Lability – correlated significantly with awakenings, as higher numbers of awakenings were associated with higher scores on the CAARS dimensions corresponding to Hyperactivity/Restlessness and Impulsivity/Emotional Lability.
While awakenings can be caused by several factors – both internal and external – the present study was conducted in a controlled environment in which external factors that may affect or interrupt sleep, such as noises or lighting conditions, were minimized and, thus, it can be reasonably inferred that the awakenings recorded in this study were spontaneous in nature. This is interesting because studies indicate that spontaneous arousals and awakenings (Muzet, 2005) occur mostly before or during REM sleep, but not SWS (Campbell, 1985; Barbato et al., 1994; Bonnet & Arand, 1997; Dijk et al., 2001), suggesting a close link between spontaneous awakenings/arousals and REM sleep. Indeed, studies have shown that REM sleep and spontaneous arousals/awakenings are regulated by the same brain structure: the PPT. As discussed in section 1.3.4.3, REM sleep is associated with activation of cholinergic neurons within the LDT/PPT and subsequent release of Ach onto key areas of the PRF, which in turn mediate some of the physiological phenomena associated with REM sleep (Lydic & Baghdoyan, 1993; Datta & Siwek, 1997). Interestingly, activation of cholinergic signaling pathways originating from the LDT/PPT is also associated with the promotion of wakefulness (Williams et al., 1994), as studies indicate that while activation of PPT cholinergic neurons leads to an increase in REM sleep, comparatively higher activation of PPT cholinergic neurons leads to increased wakefulness at the expense of REM sleep (Datta & Siwek, 1997); and, moreover, that lesions of PPT cholinergic neurons diminish or altogether eliminate cortical activation as well as REM sleep and its associated phenomena (i.e. muscle atonia and PGO waves) (Shouse & Siegel, 1992; Datta & Hobson, 1995; Datta & Siwek, 1997).

Given that in this study, the number of awakenings from sleep correlated significantly with the core symptoms of ADHD-C (i.e. Hyperactivity/Restlessness and Impulsivity/Emotional Lability) and, in turn, given that there is a link between awakenings and REM sleep, it is possible that severity in the core symptoms of ADHD-C may be related to REM sleep stability. In line with this, partial correlation analyses revealed that, in addition to the number of awakenings, Hyperactivity/Restlessness scores also correlated positively with REM sleep latency and negatively with REM sleep percentage (Table 3.15), suggesting that the mechanisms underlying the generation of REM sleep are of clinical importance to the neurobiology of ADHD-C.

Given that REM sleep and arousals/awakenings are regulated by the PPT, it is possible that in ADHD-C, abnormal regulation of cholinergic neurons within the PPT may have given rise to
increased awakenings and REM sleep latency as well as decreased REM sleep percentage; and, in turn, that these sleep disturbances may have led to exacerbation of Hyperactivity/Restlessness and Impulsivity/Emotional Lability, suggesting a causal relationship between these symptoms and REM sleep abnormalities. Indeed, evidence on associations between sleep disturbances and the development of ADHD-like symptoms has been reported extensively in the literature (see section 1.4.1).

Alternatively, Hyperactivity/Restlessness and Impulsivity/Emotional Lability correlations with REM sleep abnormalities may not be of a causal nature but, rather, the result of a common mechanism affecting both factors and specific to ADHD-C. One possibility is that abnormal regulation of cholinergic signaling may be global as opposed to localized to the PPT, and that global abnormalities in cholinergic signaling specifically associated with ADHD-C may have given rise to REM sleep abnormalities as well as Hyperactivity/Restlessness and Impulsivity/Emotional Lability. Indeed, associations between abnormal cholinergic signaling and symptoms of ADHD-C have been postulated: cholinergic activity is believed to affect striatal DA transmission (Davis & Rosenberg, 1981; Gerber et al., 2001), and in mice missing the muscarinic Ach receptor type 1, motor hyperactivity as well as elevated DA signaling in the striatum was observed (Gerber et al., 2001). Moreover, in a recent construct of ADHD, Vakalopoulos (2007) proposed that hyperactivity and impulsivity in ADHD result from abnormal dopaminergic as well as muscarinic cholinergic modulation, and although definitive evidence of global abnormalities in cholinergic signaling in ADHD-C is lacking, a recent study showed reduced muscarinic Ach receptor density in fibroblasts of boys diagnosed with ADHD-C (Johansson et al., 2013). Altogether, the results and proposals of these studies combined with my own findings suggest that cholinergic signaling may be important in the neurobiology of sleep and wakefulness in ADHD-C.

4.2.2.4 Conclusion

The results discussed in this section indicate that ADHD is associated with sleep disturbances, specifically, decreased TST and SE, and increased SOL and REML. There is also evidence to suggest that sleep in ADHD is associated with increased rates of periodic limb movements, disordered breathing, and spontaneous arousals.
Although the PSG variables of sleep measured in this study were comparable between ADHD subtypes, correlation analyses between PSG measures of sleep and the core symptoms of ADHD yielded different sets of results for the ADHD-I and ADHD-C groups, suggesting that ADHD subtypes differ with respect to how sleep is associated with daytime function.
Chapter 5
CONCLUSIONS

5.1 Limitations

There are a number of important considerations to take into account in the interpretation of the results presented herein. First, I limited this study to psychotropic medication-free subjects with no Axis-I co-morbidities with the intention of examining a “pure” ADHD sample. However, in doing so, I may have created an artificial sample that is not representative of ADHD, given that the condition is well known to be heterogeneous and associated with a slew of co-morbidities. Alternatively, results may have been affected by the presence of personality disorders, since Axis-II disorders were not assessed in this study.

Special care was taken to minimize confounding effects: age and gender were controlled for in statistical tests, and subjects taking psychotropic medications or with Axis-I co-morbidities that may affect sleep were excluded from the study. Nevertheless, it is possible that some unaccounted-for factors may have affected the results presented herein. For instance, sleep hygiene was not assessed in this study and, thus, confounding effects of poor sleep hygiene on DLMO and PSG results may have been introduced. Moreover, factors such as BMI, neck circumference, and smoking – which may affect the rate of SDB problems – were not controlled for in this study.

Another important consideration is that factors such as small sample size, unequal sample sizes in groups of comparison, low statistical power, and small effect sizes can contribute to type II errors (Berry et al., 1998). Given that there were unequal sample sizes in groups of comparison in both phase I and phase II of the study, that sample size in the analyses of DLMO data was smaller (n = 56) than the calculated required sample size (n = 68), and that the observed statistical power associated with analyses of PSG data was less than 0.80, the probability of type II error may have been high in this study.
5.2 General findings

The present study was conducted to investigate whether the ADHD Inattentive and Combined subtypes differ with respect to the nature, prevalence, and impact of sleep disturbances on the core symptoms of ADHD.

ADHD-subtype differences have previously been reported, not only in the severity of symptoms associated with hyperactivity and impulsivity, but also in the presentation of associated symptoms and co-morbidities. In this study, further ADHD-subtype differences were found in personality and character traits, as the ADHD-C phenotype was associated with high Novelty Seeking Behaviour, while the ADHD-I phenotype was associated with high Harm Avoidance. The findings fit well into neurobehavioural constructs that view ADHD as a disorder associated with abnormal regulation of mesocortical and mesolimbic signaling pathways (See Appendix VIII for in depth-discussion on this topic).

ADHD-subtype differences were also found in subjective and objective correlates of sleep. Analyses of subjective data associated with sleep revealed that a high proportion of ADHD subjects had complaints of excessive daytime sleepiness, poor sleep quality and fatigue; and that sleep quality and fatigue were worse for ADHD-I than for ADHD-C subjects. Importantly, the interrelationships between daytime sleepiness, sleep quality, and fatigue also differed between ADHD subtypes, suggesting significant differences in the interplay of sleep and wakefulness in ADHD-I and ADHD-C.

The idea that the interplay of sleep and wakefulness differs in ADHD subtypes was further supported by findings associated with objective measures of sleep. Assessment of circadian phase by DLMO testing revealed that DLMO timing is associated with inattention in subjects with ADHD-I, and with hyperactivity/impulsivity in subjects with ADHD-C – indicating ADHD subtype differences in the associations between correlates of circadian phase and the core symptoms of ADHD. Moreover, different PSG measures of sleep were found to be associated with symptoms of inattention in ADHD-I, and with symptoms of hyperactivity/impulsivity in ADHD-C – indicating ADHD subtype differences in the associations between objective measures of sleep and the core symptoms of ADHD. These findings suggest a differential role of sleep in the neuromodulation of the core symptoms of ADHD in ADHD subtypes.
Altogether, the results presented in this thesis suggest that ADHD subtype differences extend to the realm of sleep. Importantly, subtype differences lie, not in measures of sleep *per se*, but rather in the interrelationships between measures of sleep and the core symptoms of ADHD, suggesting ADHD-subtype differences in the interplay of sleep and wakefulness. This may have considerable relevance in the management and pathophysiologic understanding of ADHD in general, and it may lead to tailored treatments for the subtypes of ADHD.

5.3 A unifying theory of ADHD phenotypes – neurological mechanisms underlying sleep and wakefulness in ADHD subtypes

In this dissertation, overactivity of neurophysiologic processes in ADHD-C and neurological underarousal in ADHD-I are proposed to have implications in the differential regulation of sleep and wakefulness in ADHD subtypes.

5.3.1.1 ADHD-I and sleep

I propose that in ADHD-I, overactivity of brain networks associated with punishment-based learning leads to cortical inhibition (See Appendix VIII for in-depth discussion on this topic). Cortical inhibition, in turn, is associated with a higher than normal number of cortical columns in the sleep-like state during wakefulness, and it results in neurophysiologic underarousal and, subsequently, reduced alertness and enhanced perception of fatigue. Because cortical column states are homeostatically regulated, I speculate that fewer columns switch to the sleep-like state following neurophysiologic underarousal in wakefulness. I propose that this results in an increase in the duration of transition periods to deeper stages of sleep and, ultimately, to a lower than normal number of cortical columns in the sleep-like state during sleep, which in turn results in decreased sleep intensity, and, thus, poor sleep quality.

I speculate that the lower than normal number of cortical columns in the sleep-like state during sleep also results in fewer columns switching to the wake-like state following the sleep period, leading to an increase in the duration and intensity of the transition period from sleep to
wakefulness, thus further consolidating the underarousal and cortical inhibition promoted by overactive brain networks associated with punishment-based learning in subjects with ADHD-I (see Appendix VIII for an in-depth discussion on this topic). Inattention as a result of neurological underarousal appears to be affected by circadian phase, as DLMO time correlated with inattention scores. The association may be underlain by sleep inertia, which is a period of impaired alertness and performance immediately following awakening. The intensity and duration of sleep inertia is partly modulated by circadian cycles, and, in turn, the circadian variation of cognitive performance is strong when sleep inertia is high, and relatively weak when sleep inertia is dissipated. Given that: (i) sleep inertia is postulated to be a transitional process between sleep and wakefulness, or a continuation of the sleepy state; and that (ii) the ADHD-I subtype is marked by cortical inhibition that results in a neurological state that resembles the transitional state between sleep and wakefulness, the neurobiology of ADHD-I may set the conditions for more profound and longer effects of sleep inertia and, in this respect, higher sleep inertia may lead to stronger circadian modulation of cognitive performance and, thus, give rise to the significant associations between DLMO time and inattention scores in ADHD-I. This association is likely not to apply to the ADHD-C subtype because factors increasing neuronal activity or cerebral metabolism reduce the effects of sleep inertia, and as discussed above, the ADHD-C subtype is marked by overactivity of neurological processes.

5.3.1.2 ADHD-C and sleep

I propose that in ADHD-C, overactivity of neurophysiological processes associated with the Behavioural Activation System (see Appendix VIII for an in-depth discussion on this topic) leads to increased neuronal activity and the rapid accumulation of AD. Since AD serves as a monitor of cellular energy stores, the accumulation of AD leads to the activation of feedback mechanisms that inhibit cellular activity in order to conserve energy. Physiologically, this may manifest in the form of fatigue. Accumulation of AD also promotes the onset of sleep through inhibition of components of the ARAS and activation of the VLPO. In this manner, increases in AD levels in tandem with increased neuronal activity may lead to the activation of inhibitory feedback mechanisms that enhance the perception of fatigue and increase sleep propensity,
thereby leading to significant associations between measures of sleepiness and fatigue in subjects with ADHD-C.

I speculate that overactivity of neurophysiological processes associated with the BAS stems partly from phasic overshoot of DA due to poor regulation of DA secretion by presynaptic D₂ receptors (see Appendix VIII for an in-depth discussion on this topic). Of note, dopaminergic signaling in the striatum is highly regulated by melatonin, as melatonin antagonizes the phasic overshoot of DA by increasing the affinity of presynaptic D₂ receptors to DA, which in turn lowers phasic bursts of DA secretion, and thus reduces hyperactive/impulsive behaviours. Since melatonin concentrations only increase during the dark phase of the 24 hr. cycle, the attenuating effects of melatonin on the manifestation of hyperactive/impulsive behaviours are likely to serve the purpose of aligning sleep-wake cycles to the dark-light phases of the day by reducing neurobehavioural activity and promoting the onset of sleep. In the case of subjects with a delayed circadian phase, the attenuating effects of melatonin on dopamine signaling may extend into part of the waking life due a delayed DLMOff. And while the secretion of melatonin during the waking life is normally undesirable, it may be desirable in subjects with ADHD-C, for whom the inhibitory effects of melatonin on dopamine signaling may have attenuating effects on the manifestation of hyperactive/impulsive behaviours and, thus, have a therapeutic effect on two core symptoms of ADHD. In this regard, I propose that the extended inhibitory effects of melatonin of dopamine signaling due to a delayed DLMOff underlie the negative correlation found between DLMO time and DSM-IV-TR scores corresponding to hyperactivity/impulsivity.

5.4 Future directions

The findings of this study have opened up several avenues for investigation. These include the further characterization of ADHD subtype differences with regards to circadian cycles and sleep, through the assessment melatonin secretion profiles over a 24 hr cycle, the assessment of sleep microstructure, and the assessment of how these correlates of circadian phase and sleep are associated to the core symptoms of ADHD. Ultimately, these assessments would contribute to the overall understanding of the link between sleep and wakefulness in ADHD, and of the neurological mechanisms underlying the phenotypic differences of the Inattentive and Combined subtypes of ADHD.
Chapter 6
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APPENDICES

APPENDIX I. PUBLICATIONS

Peer-Reviewed Publications:


2. **Yoon SYR**, Jain U, Shapiro C. Objective measures of sleep and the core symptoms of attention-deficit/hyperactivity disorder in adults: subtype differences (*Submitted to Sleep*).


Textbook Chapter:

<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Classification (sample size)</th>
<th>Mean age and/or Age range</th>
<th>Medication status</th>
<th>Co-morbidity</th>
<th>Major findings</th>
<th>Strengths (S) and/or weaknesses (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ball et al., 1997&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Medicated ADHD (28) vs. non-medicated ADHD (74) vs. controls (78)</td>
<td>9 (± 2.7)</td>
<td>As noted</td>
<td>Not specified, but included LD or other emotional and/or behavioural problems</td>
<td>Medicated children reported more sleep problems and night awakenings than controls. There were no significant differences between medicated and non-medicated children with respect to reports of sleep problems.</td>
<td>S: Medication status was accounted for W: No specifications as to whether children had any potentially confounding co-morbidities, or types and doses of medications used by the medicated ADHD group.</td>
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<tr>
<td>Chervin et al., 1997&lt;sup&gt;25&lt;/sup&gt;</td>
<td>ADHD (27) vs. psychiatric controls (43) vs. healthy controls</td>
<td>9 (±4.7) 2–18</td>
<td>44% of children with ADHD were taking stimulants</td>
<td>Not specified</td>
<td>Subjects with ADHD had more habitual snoring than other groups.</td>
<td>S: Since patients were consecutively recruited, there was no recruitment bias W: Medication status or co-morbidities were not controlled</td>
</tr>
<tr>
<td>Marquette et al., 1998&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Clinical group consisting of children with ADHD and/or LD (77) vs. controls (71)</td>
<td>8.8 (±1.7)</td>
<td>Not medicated</td>
<td>LD and other psychiatric or neurologic conditions, although children with psychiatric/neurologic conditions were not included in the final clinical group</td>
<td>The clinical group scored higher on the sleep and breathing problems scale and the sleepiness scale.</td>
<td>W: Effect of LD cannot be ascertained in this study as a result of grouping of children with ADHD, children with ADHD with LD, and children with LD into the clinical group.</td>
</tr>
<tr>
<td>Ring et al., 1998&lt;sup&gt;27&lt;/sup&gt;</td>
<td>ADHD (13) vs. healthy siblings (16)</td>
<td>8.8 (±2.7) 5–13</td>
<td>All children had been taking a fixed dose of MPH for at least 4 weeks</td>
<td>All children with Axis I disorder were excluded</td>
<td>Although the mean duration of sleep in ADHD children and their siblings did not differ significantly, those with ADHD had higher rates of initial and middle insomnia, as well as nocturnal enuresis, and sleepwalking</td>
<td>W: The fact that mean duration of sleep does not differ between groups, while the rates of sleep disturbances is higher in children with ADHD reflects inaccuracies in parent reports of either sleep duration, or sleep complaints. Authors fail to discuss this issue.</td>
</tr>
<tr>
<td>Corkum et al., 1999&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Non clinical comparison group (36) vs. unmedicated ADHD (79) vs. medicated ADHD (22) vs. clinical comparison group (35)</td>
<td>9.1 6–12</td>
<td>As noted</td>
<td>Children with low IQ, PTSD, anxiety, or autism were excluded. Children included in the study had comorbidities with ODD, CD, GAD, SAD, and DEP</td>
<td>Regression analysis revealed that dysnomias and involuntary movements during sleep in children had a stronger association with medication status, comorbidity with ODD, and separation anxiety than with ADHD diagnosis.</td>
<td>S: Medicated and non-medicated children were compared in different groups. Proper control of confounding factors such as medication status and co-morbidities.</td>
</tr>
<tr>
<td>Mick et al., 2000&lt;sup&gt;19&lt;/sup&gt;</td>
<td>ADHD (122) vs. controls (105)</td>
<td>15 (±3)</td>
<td>Approximately half of the ADHD group was on stimulant medication</td>
<td>Mood disorders, anxiety, CD/ODD</td>
<td>Mood disorders, anxiety, CD/ODD</td>
<td>S: Statistical analyses taking medication status and co-morbidities into account.</td>
</tr>
<tr>
<td>Owens et al., 2000&lt;sup&gt;20&lt;/sup&gt;</td>
<td>ADHD (46) vs. controls (46)</td>
<td>5–10</td>
<td>Not medicated</td>
<td>ODD, CD, LD</td>
<td>Children with ADHD had increased rates of bedtime resistance, sleep onset delays, night awakenings, parasomnias, and daytime sleepiness; and decreased sleep duration.</td>
<td>W: Small sample size led to inability to assess whether co-morbid disorders in some of the children with ADHD played a role in the development of sleep problems.</td>
</tr>
<tr>
<td>Authors, year of publication</td>
<td>Classification (sample size)</td>
<td>Mean age and/or Age range</td>
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<td>Major findings</td>
<td>Strengths (S) and/or weaknesses (W)</td>
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<td>Stein et al., 2002&lt;sup&gt;44&lt;/sup&gt;</td>
<td>Medicated ADHD (17) vs. unmedicated ADHD (18) vs. control (40) children</td>
<td>13–16</td>
<td>As noted</td>
<td>Children with Axis I disorders were excluded from the study. However, children with CD, ODD, and mild anxiety or depression may have been inadvertently included in the study.</td>
<td>Medicated adolescents with ADHD had increased rates of moderate to severe sleep disturbances compared to non-medicated adolescents with ADHD and controls. However, sleep disturbances in medicated adolescents were associated with depression, rather than with ADHD diagnosis, while in the non-medicated group, sleep disturbances were associated with anxiety.</td>
<td>S: Medication status and confounding effects of anxiety and depression taken into account. W: Relatively small sample size.</td>
</tr>
<tr>
<td>LeBourgeois et al., 2004&lt;sup&gt;42&lt;/sup&gt;</td>
<td>ADHD-I (21) vs. ADHD-HI (24) vs. ADHD-C (16) vs. controls (29)</td>
<td>6–16</td>
<td>Some children were taking stimulant or hypnotic medications</td>
<td>Children with learning disabilities were excluded from the study. Comorbidities included depression, OCD, ODD, and BD</td>
<td>A higher percentage of children with ADHD suffered from daytime sleepiness, poor sleep quality, initial insomnia, and trouble waking up in the morning compared to controls. Among subtypes, ADHD-HI children scored more and had a tendency towards more trouble going to bed than their ADHD-C counterparts. No other differences were reported between ADHD subtypes.</td>
<td>S: Comparison of ADHD subtypes. W: Presence and influence of comorbidities and/or medication status were not taken into account in the data analysis.</td>
</tr>
<tr>
<td>Gau et al., 2005&lt;sup&gt;43&lt;/sup&gt;</td>
<td>Children with T-score &gt; 60 (414) vs. T ≤ 60 (2047) according to the CPRS-RS and T &gt; 60 (318) vs. T ≤ 60 (2145) according to the CRF-RS</td>
<td>11.6 (±2.6) 6–16</td>
<td>Not specified</td>
<td>Not specified</td>
<td>According to parent reports using the CPRS-RS, children with T-score ≤ 60 had more differences in bedtime in weekdays and weekends, and more sleep problems such as dyssomnia, parasomnia, SDB, and inadventent daytime naps than children with T-score &gt; 60. According to teacher reports using the CRF-RS, children with T-score &gt; 60 had later rise times on weekdays, shorter sleep time on weekends, and more sleep problems such as dyssomnia, SDB, and inadventent daytime naps than children with T-score ≤ 60.</td>
<td>W: No information on medication status or co-morbidities.</td>
</tr>
<tr>
<td>Lim et al., 2008&lt;sup&gt;44&lt;/sup&gt;</td>
<td>ADHD (101) vs. controls (60)</td>
<td>5–13</td>
<td>Not clearly specified. 41/114 ADHD children had been prescribed medications, but only the data for 101 children were included in the statistical analyses</td>
<td>Other than aggression problems, externalizing problems, and delinquent behaviours in some of the subjects in either group, not specified</td>
<td>Subjects in the ADHD group were reported to sleep less than subjects in the control group.</td>
<td>W: No information as to comorbidities in subjects. Also, although it is claimed by authors that interviewed subjects did not appear to have significant sleep complaints as a result of medication, medication status in the studied groups not clearly specified.</td>
</tr>
<tr>
<td>Sung et al., 2008&lt;sup&gt;45&lt;/sup&gt;</td>
<td>ADHD (239)</td>
<td>11.7 (±3.2) 5–18</td>
<td>About 80% of the study subjects were taking medications (ADHD meds, clonidine, and other)</td>
<td>LD, ODD, CD, depression and/or anxiety, Asperger disorder, other</td>
<td>About 30% of children with ADHD had mild sleep problems and about 45% had moderate to severe sleep problems such as trouble falling asleep, bedtime resistance, difficulty getting up, night wakeuings, restless sleep, breathing difficulty during sleep, and tiredness on waking.</td>
<td>W: Effects of medication status and co-morbidities not taken into account in statistical analyses.</td>
</tr>
</tbody>
</table>
Subjective Sleep in Children with ADHD

Hvolby et al., 2009

ADHD (45) vs. clinical control (64)
vs. healthy control (212)
5–11 No
ODD, CD, emotional disorders, other
No significant differences were found between clinical controls and healthy controls. On the other hand, ADHD children were found to have more sleep problems such as bedtime resistance, difficulty falling asleep, restless sleep, sleep talking, teeth grinding, nightmares, and difficulty waking in the morning. Moreover, sleep onset latency was higher in the ADHD group in comparison to clinical and healthy controls.

Li et al., 2009

ADHD (853) vs. controls (19299)
9 (±1.6)
5–11 MPH
Children with anxiety, depression, or LD excluded from study
A multiple regression model controlled for age, gender, and medication status revealed that history of ADHD correlated significantly with sleep problems such as bedtime resistance, sleep onset delay, sleep anxiety, nighttime awakenings, parasomnia, SSR, and daytime sleepiness.

S: Medication status was controlled for, and given exclusion of children with co-morbid anxiety/depression/LD, comorbidities were somewhat controlled for.

Mayes et al., 2009

ADHD-C (271) vs. ADHD-I (144)
vs. ADHD-C with ODD (102)
vs. ADHD-C with anxiety or depression (79)
vs. ADHD-C with ODD and anxiety or depression (43)
6–16 212 children treated with medication
ODD, Anxiety disorder, and depression
While ADHD-I children did not differ from controls, ADHD-C children had more sleep problems than ADHD-I (trouble falling asleep, restless sleep, night awakenings) and control children with anxiety or depression (trouble falling asleep, sleeping less than normal).

S: Stratification of ADHD children into ADHD subtypes and ADHD subtypes with co-morbidities, as well as medication status. W: In determining correlations between ADHD severity and T-scores of sleep problems, authors did not stratify data into subtypes. Considering that ADHD severity is determined by the addition of scores on inattentive and hyperactive/impulsive symptomatology, it would have been interesting to see whether the correlation between ADHD severity and sleep problems holds when groups are stratified into ADHD subtypes.

ADHD = Attention-deficit/hyperactivity disorder, ADHD-C = ADHD of the combined subtype, ADHD-I = ADHD of the hyperactive/impulsive subtype, ADHD-H = ADHD of the inattentive subtype, BD = bipolar disorder, CD = conduct disorder, DEP = major depressive episode, C(PT)RS-R:S = Conner’s (parent/teacher) rating scale-revised: short forms, GAD = generalized anxiety disorder, IQ = intelligence quotient, LD = learning disability, MPH = methylphenidate, ODD = obsessive compulsive disorder, ODD = oppositional defiant disorder, PTSD = post-traumatic stress disorder, SAD = separation anxiety disorder, SD = standard deviation.
<table>
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<th>Authors, year of publication</th>
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<th>Mean age and/or Age range</th>
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<th>Strengths (S) and/or weaknesses (W)</th>
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<tr>
<td>Busby et al., 1981&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Hyperkinetic children (11) vs. controls (11)</td>
<td>8–12</td>
<td>Not medicated</td>
<td>Children with major psychosis, overanxiety, or unsocialized aggressive behaviour were excluded from the study.</td>
<td>PSG, five nights: Increased REM sleep latency in hyperkinetic group.</td>
<td>S: Multiple nights of PSG. W: Classification of hyperkinesis is likely to be somewhat different from what ADHD is defined as at present.</td>
</tr>
<tr>
<td>Palm et al., 1992&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Children with deficits in attention, motor control, and perception (DAMP) (9) vs. controls (16)</td>
<td>6.3–12.3</td>
<td>Not medicated</td>
<td>Children with severe neurotic or psychotic disorders were excluded from the study.</td>
<td>PSG, two nights: On the second night of recordings, DAMP children had small increases in TSP, REM percentage, SOL, and REM sleep latency, and a small decrease in S1 sleep percentage. In three of the DAMP children, SOL was decreased in MSLT, suggesting daytime sleepiness.</td>
<td>S: Two nights of PSG. W: Small sample size</td>
</tr>
<tr>
<td>Gnuber et al., 2000&lt;sup&gt;13&lt;/sup&gt;</td>
<td>ADHD (38) vs. control children (64)</td>
<td>9 (±2) 6–14</td>
<td>Not medicated</td>
<td>Children with behavioural problems and LD were excluded from the study.</td>
<td>PSG: five nights: While there were no significant differences on SOT, sleep duration, or true sleep between ADHD and control groups, the standard deviations of these parameters were significantly different between groups, suggesting increased night to night variability in ADHD.</td>
<td>S: Interesting take, looking at night-to-night variation rather than averaged outcomes for the analysis of sleep parameters in the studied groups. W: Study consisted of boys only</td>
</tr>
<tr>
<td>Corkum et al., 2001&lt;sup&gt;51&lt;/sup&gt;</td>
<td>ADHD (25) vs. controls (25)</td>
<td>9 (± 1.3) 7–11</td>
<td>Not medicated</td>
<td>ODD, CD, GAD, SAD, MD</td>
<td>Actigraphy, seven nights: Although parents reported increases in sleep duration, SOL, restless sleep, bedtime resistance, and difficulties arising in the morning in ADHD, actigraphy revealed no significant differences between groups.</td>
<td>S: Eliminated possible confounding effect of collapsing all the week data by stratifying data into weekday and weekend variables. W: Co-morbidities were not controlled for, which may have masked possible differences between ADHD and controls.</td>
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<tr>
<td>Konofal et al., 2001&lt;sup&gt;52&lt;/sup&gt;</td>
<td>ADHD (30) vs. controls (30)</td>
<td>5–10</td>
<td>Not medicated</td>
<td>Children with psychotic disorders were excluded from the study.</td>
<td>PSG and video recording, one night: No significant differences between ADHD children and controls, although video recordings revealed more limb movements in ADHD children.</td>
<td>S: Additional information gained from the video recording, without which the conclusion would have been that ADHD children and controls do not differ in variables of sleep. W: This study was a chart review, thus, medication status or comorbidities were not properly controlled for. Also, only the data for one night of PSG recordings were available for each child.</td>
</tr>
<tr>
<td>Crabtree et al., 2003&lt;sup&gt;33&lt;/sup&gt;</td>
<td>ADHD (97)</td>
<td>8.3 (± 3) 3–18</td>
<td>Stimulants, other psychotropic agents, and sleep promoting agents</td>
<td>Non-specified co-morbidities</td>
<td>PSG, one night in 69 children: 7% had SDB, 36% had PLMS-5, and 6% had sleep fragmentation. No other abnormalities found in the averaged means of sleep variables.</td>
<td>Actigraphy, 14 days in 16 children: Significant night to night variability. Subjective data: Children with significant and mild ADHD symptoms had more enuresis and snoring compared to controls. Children with significant ADHD symptoms had more restless sleep, awakenings, talking, teeth grinding, difficulties initiating sleep, daytime sleepiness, and unwillingness to go to sleep. PSG, one night: Children with significant ADHD symptoms had increased REM sleep latency and decreased REM sleep percentage compared to controls.</td>
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<tr>
<td>O’Brien et al., 2003&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Children with significant ADHD symptoms (44) vs. children with mild ADHD symptoms (27) vs. controls (39)</td>
<td>5–7</td>
<td>Not specified, but likely medication free</td>
<td>Children with psychiatric diagnoses were excluded from the study.</td>
<td>PSG, one night: Children with significant ADHD symptoms had increased REM sleep latency and decreased REM sleep percentage compared to controls.</td>
<td>S: This study was a chart review, thus, medication status or comorbidities were not properly controlled for. Also, only the data for one night of PSG recordings were available for each child. W: Only one night of PSG.</td>
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<tr>
<td>Reference</td>
<td>Study Details</td>
<td>Objective Sleep in Children with ADHD</td>
<td>Subjective Data</td>
<td>Additional Notes</td>
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<td>O'Brien et al., 2003</td>
<td>Clinical sample of children with ADHD (ADHDcl) (47) vs. community sample of children with ADHD (ADHDcom) (53) vs. controls (49)</td>
<td>Clinical ADHD sample 8 (±1.6) Community ADHD sample 6.6 (±0.4) Controls 6.7 (±0.4)</td>
<td>72% and 51% were medicated in the clinical and community ADHD sample, respectively</td>
<td>Children with psychiatric diagnoses were excluded from the study</td>
<td>More difficulties initiating sleep, restless sleep, nightmares, and EDS in ADHDcl and ADHDcom; and increased sleep walking, enuresis, and stops in breathing in ADHDcl. PSG, one night: ADHDcl and ADHDcom had increased REM sleep latency and decreased REM sleep percentage. ADHDcl had increased SWS and PLMI, and decreased spontaneous arousal index. Subjective Data: ADHD children had nightmares and nocturnal enuresis. A higher percentage of medicated children had restless sleep. PSG, one night: Children with ADHD had decreased REM sleep percentage in comparison to controls. Also, ADHDmed children had increased TST. PSG, one night: The ADHD group had increases in REM sleep percentage, arousal index, RDI, number of children with SDB, and number of children with PLMD compared to controls. MSLT revealed that children with ADHD are sleepier than controls.</td>
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<tr>
<td>O'Brien et al., 2003</td>
<td>Medicated ADHD (ADHDmed) (53) vs. unmedicated ADHD (ADHDonon) (34) vs. controls (53)</td>
<td>3–11</td>
<td>As indicated. 60% of ADHDmed were taking MPH and 40% were taking DEX</td>
<td>Not specified</td>
<td>No specification of comorbidities and only one night of PSG</td>
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<tr>
<td>Golan et al., 2004</td>
<td>ADHD (34) vs. controls (32)</td>
<td>12 (±3.6)</td>
<td>Stimulant medication free for 3 days prior to study</td>
<td>Not specified</td>
<td>No specification of comorbidities and only one night of PSG</td>
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<tr>
<td>Gruber and Sadeh, 2004</td>
<td>ADHD (24) vs. controls (25)</td>
<td>7–11</td>
<td>Not medicated</td>
<td>No comorbidities</td>
<td>Actigraphy, five days: Higher night to night variability in variables such as sleep onset time, TST, and true sleep time in the ADHD group. PSG, one night: Children had increased S3 sleep percentage and AHI, and decreased mean saturated oxygen (SaO2). Closer inspection of AHI values revealed a higher percentage of ADHD children with AHI &gt; 1, suggesting a higher prevalence of SDB in these children. Also, a higher percentage of children with ADHD had PLMI &gt; 5 than controls.</td>
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<td>Huang et al., 2004</td>
<td>ADHD (88) vs. controls (27)</td>
<td>9</td>
<td>Not specified, but most likely not medicated</td>
<td>Exclusion of children with a history of BD, psychosis, anxiety, seizure disorder, substance abuse, or mental retardation</td>
<td>No specification of comorbidities and only one night of PSG.</td>
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<tr>
<td>Kirov et al., 2004</td>
<td>ADHD (17) vs. controls (17)</td>
<td>11 (±2) 8–14</td>
<td>Not medicated</td>
<td>Dyslexia, CD, panic disorder, nocturnal enuresis</td>
<td>No specification of comorbidities and only one night of PSG.</td>
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<tr>
<td>Sangal et al., 2005</td>
<td>ADHD (40)</td>
<td>6–14</td>
<td>Not medicated</td>
<td>Children with primary sleep disorders or psychiatric diagnosis were excluded from the study</td>
<td>No specification of comorbidities and only one night of PSG.</td>
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<tr>
<td>Wiggs et al., 2005</td>
<td>ADHD-I (8) vs. ADHDIII (19) vs. ADHD-C (23) vs. controls (21)</td>
<td>3–15</td>
<td>Not medicated</td>
<td>Antisocial behaviour, emotional symptoms, peer problems, CD, autism</td>
<td>Actigraphy, five nights: Other than some discrepancies between subjective reports of parents and objective data obtained from actographies on SOT (parents of ADHD-I children reported earlier SOT than what was revealed by actigraphy), there were no significant differences between ADHD subtypes. SDB, sleeplessness as a result of poor sleep hygiene, and RLS appeared to be common in ADHD.</td>
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</table>

**W**: Only one night of PSG.  
**S**: Stratification of ADHD into subtypes, even though no differences were found between subtypes.  
**W**: Small sample sizes.
<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Classification (sample size)</th>
<th>Mean age and/or Age range</th>
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<tr>
<td>Miano et al., 2006&lt;sup&gt;23&lt;/sup&gt;</td>
<td>ADHD (20) vs. controls (20)</td>
<td>6–13</td>
<td>Not medicated</td>
<td>LD, language disorders, and mild neurologic signs</td>
<td>PSG, two nights: In comparison to controls, the ADHD group had decreases in time spent in bed, sleep period time, TST, and an increase in stage shifts. Also, decreases in CAP rate were found in stage 2 of NREM sleep.</td>
<td>S: Using micro-architecture variables of sleep may be a new window for the investigation of the sleep disturbances in ADHD, which may explain contradictions between subjective and objective data in reports of sleep problems in subjects with ADHD. W: For the time being, however, the use of micro-architecture variables of sleep is not well established for investigating sleep disturbances.</td>
</tr>
<tr>
<td>Van der Heijden et al., 2006&lt;sup&gt;24&lt;/sup&gt;</td>
<td>ADHD with sleep onset insomnia (SOI) vs. ADHD without SOI (33)</td>
<td>6–12</td>
<td>Not medicated</td>
<td>Disruptive behavioural disorder, anxiety disorder, and affective disorder</td>
<td>Actigraphy, five days: Significant delays in the SOI group with regards to DLMO time, sleep latency, sleep onset, wake up, and get up times.</td>
<td>S: Control for ADHD subtype and co-morbidities in statistical analyses. W: Although authors state that 87 ADHD-SOI children were compared to 33 ADHD-noSOI children, DLMO data were only available for 78 out of 87 ADHD-SOI children and 33 out of 33 ADHD-noSOI children. Demographics for these new groups may have been different from those published in the paper, which may have introduced confounding errors to the study. Also, the sleep onset time used to define sleep onset delay has been deemed too early by other groups.</td>
</tr>
<tr>
<td>Silvestri et al., 2007&lt;sup&gt;25&lt;/sup&gt;</td>
<td>ADHD (42)</td>
<td>8.9 (±2.8)</td>
<td>Not medicated</td>
<td>ODD, dyslexia, tic disorder, eating disorder, dyspraxia</td>
<td>PSG, one night: Increased prevalence of sleep disorders such as icctal and interictal epileptiform discharges, RLS, sleep related movement disorders, arousals, and SDB.</td>
<td>S: Use of Spearman correlation coefficients to assess association between, among others, comorbidities and variables of sleep such as EEG and sleep efficiency. W: Only one night of PSG.</td>
</tr>
<tr>
<td>Hvolvy et al., 2008&lt;sup&gt;14&lt;/sup&gt;</td>
<td>ADHD (45) vs. psychiatric controls (64) vs. healthy controls (97)</td>
<td>6–11</td>
<td>Not medicated</td>
<td>ODD, CD, emotional disorders, other</td>
<td>Actigraphy, seven nights: Although parents of children with ADHD overestimated SOL, actigraphy revealed that these children had the highest SOL in comparison to psychiatric and healthy controls. Stratification into ADHD children with and without ODD revealed that ODD is not associated with increases in SOL in ADHD.</td>
<td>S: Control for co-morbidities such as ODD and anxiety.</td>
</tr>
<tr>
<td>Goraya et al., 2009&lt;sup&gt;16&lt;/sup&gt;</td>
<td>ADHD (33)</td>
<td>3–6</td>
<td>48% of children were on stimulant medication</td>
<td>Not specified</td>
<td>PSG, one night: Increases in arousal index, wake after sleep onset, and daytime sleepiness; and decrease in sleep efficiency were observed in children with ADHD in comparison to reference values. Also, with a threshold value set at AH{H} = 1/hour, 64% of children with ADHD met criteria for SDB.</td>
<td>S: Stratification of group into ADHD children with and without SDB revealed that ADHD children with SDB had increases in SOL, REM latency, wake after sleep onset, arousal index, and AH; and decreases in REM percentage, SE, and O2 saturation. W: One night of PSG. Also, neither comorbidities nor medication status were controlled for.</td>
</tr>
<tr>
<td>Gruber et al., 2009&lt;sup&gt;27&lt;/sup&gt;</td>
<td>ADHD (15) vs. controls (23)</td>
<td>7–11</td>
<td>Not medicated</td>
<td>Children with any psychiatric diagnosis excluded from study</td>
<td>PSG, one night: Decreases in the ADHD group with respect to TST and REM percentage. According to parental reports, children with ADHD had more sleep onset delays and anxiety compared to controls.</td>
<td>W: Relatively small sample size, and only one night of PSG.</td>
</tr>
<tr>
<td>Study</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Medication</td>
<td>Objective Sleep Description</td>
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<tr>
<td>Owens et al., 2009&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>ADHD (107) vs. controls (46)</td>
<td>6–14</td>
<td>Not medicated</td>
<td>While patients with ODD were included; patients with BD, affective or anxiety disorder, or a history of primary sleep disorders were excluded from the study. Parent Reports: ADHD children had more difficulties getting up, transitioning in the evening, getting ready for bed and falling asleep. Child Diary Reports: ADHD children had more difficulties getting up in the morning, poorer sleep quality, and more daytime sleepiness. Actigraphy, five days: Although ADHD and controls did not differ in TST, ADHD children had decreased real sleep time, likely due to more interruptions during sleep.</td>
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<tr>
<td>Silvestri et al., 2009&lt;sup&gt;c&lt;/sup&gt;</td>
<td>ADHD (55) vs. controls (20)</td>
<td>8.9 (±2.7)</td>
<td>Not specified</td>
<td>ODD, dyslexia, language disorder, tic disorder, eating disorder, and dyspraxia were compared. Parent Reports: ADHD children had decreases in TST, SE, and REM sleep; and increases in stage 3 NREM sleep, arousal index, and REM latency. When data were stratified into ADHD-I and ADHD-II/C children, PLMS index was found to be higher in ADHD-II/C children.</td>
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</tbody>
</table>

<sup>a</sup> ADHD = Attention deficit hyperactivity disorder, BD = bipolar disorder, ODD = oppositional defiant disorder, CD = conduct disorder, DEX = dextro-amphetamine, DLM = dim light melatonin onset, GAD = generalized anxiety disorder, LD = learning disability, MD = major depression, MPH = methylphenidate, MSLT = multiple sleep latency test, ODD = oppositional defiant disorder, PLMS = periodic limb movement index, RDI = respiratory disturbance index, REM = rapid eye movement, SI = stages 1 sleep, SAD = separation anxiety disorder, SDB = sleep disordered breathing, SE = sleep efficiency, SOL = sleep onset latency, SOT = sleep onset time, TST = total sleep time.

<sup>b</sup> In addition to comparisons of ADHD with healthy controls, sleep variables were compared in children with Mild/Moderate and Severe forms of ADHD; as well as in inattentive and combined subtypes of ADHD. However, no significant differences were found between the comparison groups. Child diary reports were included in the study thus avoiding complete reliance on parental reports.

<sup>c</sup> Although at least one night of video PSG was recorded, it is not clear exactly how many nights each child was recorded for and, thus, whether the "first night effect" was taken into consideration when analyzing data. Also, medication status in the study sample was not specified, suggesting that the confounding effects of mixed medication status may have been an issue in data analysis. Lastly, although a percentage of the study sample suffered from various co-morbidities, they were not controlled for in data analysis.
### APPENDIX IV. STUDIES OF SLEEP IN ADULTS WITH ADHD BY SUBJECTIVE METHODOLOGIES.

<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Classification (sample size)</th>
<th>Mean age and/or Age range</th>
<th>Medication status</th>
<th>Co-morbidity</th>
<th>Major findings</th>
<th>Strengths (S) and/or weaknesses (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangal and Sangal, 2004&lt;sup&gt;10&lt;/sup&gt;</td>
<td>ADHD (18) vs. subjects with complaints of snoring and sleepiness (38)</td>
<td>48.7 (±15.5) for sleep disorder patients 31.9 (±12.2) for ADHD</td>
<td>Not specified</td>
<td>Not specified</td>
<td>ADHD subjects had a significantly lower ESS score than sleep disordered subjects. With a mean score of 8.3, ADHD subjects did not meet criteria for EDS. ESS score was not found to correlate with inattention or hyperactivity/impulsiveness scores in ADHD subjects.</td>
<td>W: Relatively small sample size</td>
</tr>
<tr>
<td>Oosterloo et al., 2006&lt;sup&gt;30&lt;/sup&gt;</td>
<td>ADHD (61) vs. narcolepsy (67) vs. Idiopathic Hypersomnia (81) (7) ADHD-L subdivided into ADHD (53) vs. probable ADHD (486) vs. non-ADHD (1745); and ADHD-HL subdivided into ADHD (16) vs. probable ADHD (130) vs. non-ADHD (2138)</td>
<td>48.45 (±16.21) for LH patients 34.98 (±10.28) for ADHD patients 19.3 (±2.7)</td>
<td>Not medicated at the beginning of the study</td>
<td>Not specified</td>
<td>Approximately 38% of ADHD patients met criteria for excessive daytime sleepiness (EDS), compared to 96% in LH patients.</td>
<td>W: Co-morbidities and medication status were not clearly specified or controlled for</td>
</tr>
<tr>
<td>Gau et al., 2007&lt;sup&gt;71&lt;/sup&gt;</td>
<td>ADHD (120, out of whom 61 were medicated or co-morbidity free) vs. controls (444)</td>
<td>34.78 (±10) for medicate d ADHD 35.3 (±10.8) for nonmedicate d ADHD 23.5 (±5.7) for controls</td>
<td>As noted. Medications included MPH, reboxetine, serotonine reuptake inhibitors, venlafaxine, tricyclic antidepressants and fenfluramine</td>
<td>As noted, including depression or dysthymia, anxiety, tic disorder, OCD, and current substance abuse</td>
<td>ADHD-I group: Differences reported in sleep need and number of sleep problems between ADHD, probable-ADHD and non-ADHD subgroups, with ADHD subgroup having the highest number of needed sleep hours and sleep problems, both current and lifetime. Significant sleep problems in ADHD and probable-ADHD subgroups included early and middle insomnia, sleep talking, nightmares, and snoring. ADHD-H group: Differences reported in the number of sleep problems between ADHD, probable-ADHD, and non-ADHD subgroups, with ADHD subgroup having the highest number of sleep problems, both current and lifetime. Significant sleep problems in ADHD and probable-ADHD subgroups included early insomnia, sleep terrors, and snoring.</td>
<td>W: Though compelling due to the large sample size, the analysis of data could have yielded interesting results, had it been stratified so as to compare ADHD subtypes. Also, neither medication status nor co-morbidities were specified or controlled for in statistical analyses.</td>
</tr>
<tr>
<td>Schredl et al., 2007&lt;sup&gt;72&lt;/sup&gt;</td>
<td>ADHD (182) vs. controls (117)</td>
<td>18–55</td>
<td>Not specified</td>
<td>MDD, mania, separation anxiety, agoraphobia, panic disorder, OCD, GAD, specific phobias, PTSD, social phobia, and substance use</td>
<td>In comparison to controls, ADHD subjects had lower sleep quality, un-refreshing sleep, insomnia, increased SOL and nocturnal awakenings, problems with sleep quality and sleep/wake patterns, nocturnal breathing disorders, parasomnias, movement disorders, and felt more tired during the day. Of note, movement disorders, insomnia, problems with sleep quality and sleep/wake disorders, parasomnias, and tiredness during the day were found to be associated with depression scales, rather than with ADHD scales; while comorbidity with depression appeared to be associated with insomnia, poor sleep quality, and feeling un-refreshed in the morning. Medication status did not appear to affect the presence or severity of sleep problems.</td>
<td>S: Multiple statistical analyses taking into consideration comorbidities, severity of comorbidities, and medication status.</td>
</tr>
<tr>
<td>Surman et al., 2008&lt;sup&gt;73&lt;/sup&gt;</td>
<td>ADHD (251) vs. controls (117)</td>
<td>18–55</td>
<td>Not specified</td>
<td>MDD, mania, separation anxiety, agoraphobia, panic disorder, OCD, GAD, specific phobias, PTSD, social phobia, and substance use</td>
<td>Compared to controls, ADHD subjects had more difficulties going to sleep, waking up in the morning, restless sleep, sleep talking, nightmares, and repetitive actions in sleep; and increases in sleep latency, nocturnal awakenings, and daytime sleepiness. Controlling for medication status and co-morbidities, it was found that the associations between ADHD and sleep disturbances still hold.</td>
<td></td>
</tr>
<tr>
<td>Caci et al., 2009&lt;sup&gt;24&lt;/sup&gt;</td>
<td>ADHD (204)</td>
<td>Adults 42.18 (±11.46) Students 27.33 (±8.81)</td>
<td>Not specified</td>
<td>Not specified</td>
<td>A negative association was found between scores for the CSM and inattention in the ASRS, suggesting that there may be ADHD subtype differences with respect to circadian preference, with the inattentive subtype being more of an evening type.</td>
<td>W: No specification of medication status or co-morbidities</td>
</tr>
</tbody>
</table>

**ADHD** — attention-deficit/hyperactivity disorder, **ADHD-C** — ADHD of the combined subtype, **ADHD-HI** — ADHD of the hyperactive/impulsive subtype, **ADHD-I** — ADHD of the inattentive subtype, **ASRS** — adult self report scale. **CSM** — composite scale of morningness, **EDS** — excessive daytime sleepiness, **ESS** — Epworth sleepiness scale, **IH** — idiopathic hypersomnia, **GAD** — generalized anxiety disorder, **MDD** — major depressive disorder, **MPH** — methylphenidate, **OCD** — obsessive compulsive disorder, **PTSD** — post-traumatic stress disorder.
<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Classification (sample size)</th>
<th>Mean age and/or Age range</th>
<th>Medication status</th>
<th>Co-morbidity</th>
<th>Major findings</th>
<th>Strengths (S) and/or weaknesses (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kooij et al., 2001⁷⁵</td>
<td>ADHD (8) vs. controls (8)</td>
<td>21–44</td>
<td>All subjects started medication free. Then, 7 patients were treated with MPH, and one patient was treated with DEX</td>
<td>Dependent personality disorder, dysthymia, eating disorder, borderline personality disorder, MDD</td>
<td>Actigraphy, six nights: At baseline, ADHD subjects had poorer sleep quality and increased activity level and movement index in comparison to controls. After three weeks of medication, sleep quality improved, and movement index decreased in ADHD subjects.</td>
<td>W: Given the small sample size of this study, it is difficult to ascertain what the role of co-morbidities is in the sleep disturbances. Also, the fact that the mean activity level increased in the control group after 3 weeks somewhat undermines the significant differences found between baseline and week 3 in the ADHD group. It should be noted, however, that to account for the small sample size of this study, authors set the level of statistical significance at 0.10.</td>
</tr>
<tr>
<td>Phillipsen et al., 2005⁷⁶</td>
<td>ADHD (20) vs. controls (20)</td>
<td>33.45 (±8.94) 22–55</td>
<td>Not medicated</td>
<td>Lifetime, but not current, history of drug abuse, BRD, MDD, agoraphobia, bulimia nervosa</td>
<td>PSG, two nights: No differences between ADHD and control subjects. Subjectively, adults with ADHD reported poorer sleep quality, lower restorative value of sleep, worse mood in the evening, and more fatigue and psychosomatic symptoms during sleep onset.</td>
<td>S: The data for two nights of PSG were used in statistical analysis to assess night (adaptation and baseline) and group (ADHD and controls) interactions. W: Relatively small sample size.</td>
</tr>
<tr>
<td>Boonstra et al., 2007⁷⁷</td>
<td>ADHD (33) vs. controls (39)</td>
<td>37 (±10)</td>
<td>MPH for drug trial</td>
<td>Depression and anxiety</td>
<td>Actigraphy, seven nights: ADHD subjects had lower SE and increased SOL compared to controls. Effects of MPH treatment included decreases in nocturnal awakenings, time in bed, actual sleep; increased sleep onset latency; and delayed sleep bedtime. Correlation tests revealed no associations between comorbidities and sleep variables.</td>
<td></td>
</tr>
<tr>
<td>Sobanski et al., 2008⁷⁸</td>
<td>ADHD (34) vs. controls (34)</td>
<td>35 (±9)</td>
<td>16 ADHD patients were treated with MPH as part of the study</td>
<td>Combined motor and tic disorder, social phobia, and dysthymia, all mild forms</td>
<td>PSG, two nights: In comparison to controls, all ADHD subjects had decreased SE and REM sleep; and increased nocturnal awakenings and stage 1 sleep percentage. ADHD subjects free of comorbidities exhibited lowered SE, duration of first REM sleep period, and REM sleep percentage; and higher nocturnal awakenings and percentage of sleep in the wake state were reported. After a four week treatment with MPH, ADHD subjects showed improvements in SE and decreased SOL.</td>
<td>S: The effects of medications and co-morbidities on sleep disturbances and complaints in ADHD were well controlled for.</td>
</tr>
</tbody>
</table>

DEX = dextro-amphetamine, BRD = brief recurrent depression, MDD = major depressive disorder, MPH = methylphenidate, PSG = polysomnography, REM = rapid eye movement, SE = sleep efficiency, SOL = sleep onset latency.
APPENDIX VI. CONSENT FORM 173/2009

Name of Study: Adults with Attention Deficit Hyperactivity Disorder (ADHD): A New Cohort Sample Using an Updated Protocol

Responsible Investigators: Dr. Umesh Jain, MD, PhD 416-979-4953

I, __________, agree to participate in this study which is being conducted by Dr. Umesh Jain, the Principal Investigator. The purpose, benefits, risks and methods have been explained to me by __________.

Purpose: The purpose of this study is to better understand ADHD. This may lead to a greater knowledge of what causes ADHD, to make better diagnoses, to clarify other causes and to improve treatments.

Procedures: You will be asked to fill out a very detailed questionnaire, CADDRA Adult ADHD Checklist. The last page of the questionnaire asks you to obtain some information from a source that knows you well. There will be other questionnaires (e.g. DSM-IV checklist, the Adult ADHD Self Report Scale, the Temperament and Character Inventory and other standard symptom checklists) which, in their entirety, may take about one and half hours to complete. These are part of the normal evaluation and are important to help make the diagnosis. Fill out each question even though some are similar on the different questionnaires but they are scored separately.

Risks and Benefits: The possible risks to you may include feelings of upset evoked by answering questions that may be sensitive issues. The level of difficulty you will have should not be any greater than seeing your family doctor. There are no direct benefits to you though making the symptoms clearer may have certain gains for future treatment strategies for you. These same questionnaires, when used in follow-up studies, that you may be asked to participate in, will help to determine long-term outcome and the utility of current practices. Any information obtained in any questionnaires, the interview or participation in any future research will be kept in strict confidence. Your name will never be used in any publication, communication or research paper.

Confidentiality: Your identity will be kept confidential to the full extent provided by law. In addition, neither your name nor any other personal identifier will be used in any reports or publications arising from this study. As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by the Health Canada Therapeutic Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law.

Subject’s Initials __________________

Approved CAMH REB
FEB 12 2010
APPENDIX VI (CONTINUED). CONSENT FORM 173/2009

Adult ADHD Study: Umesh Jain 2010

Voluntary Participation: You understand that you can withdraw your consent to participate in this study at any time without affecting your future treatment at the Centre for Addiction and Mental Health. If you have questions about the study that are not answered in this Consent, you should ask them.

AGREEMENT TO PARTICIPATE

I, __________________, have read (or had read to me) the Consent Form for the study named ‘Adults with Attention Deficit Hyperactivity Disorder (ADHD): A New Cohort Sample Using an Updated Protocol’. The purpose of this study is to gather vital information on ADHD. My role in the study is as a research volunteer to help the investigators collect information about ADHD. My questions, if any, have been answered to my satisfaction. By signing this consent form I do not waive any of my rights. Dr. Padraig Darby, Chair, Research Ethics Board, Centre for Addiction and Mental Health, may be contacted by research subjects to discuss their rights. Dr. Darby may be reached by telephone at 416-535-8501 ext. 6876.

I agree to participate.

Research Volunteer:

Signature: ____________________________

Date: ____________________________

Name: ____________________________

Please Print

Person Obtaining Consent:

Signature: ____________________________

Date: ____________________________

Name: ____________________________

Please Print
APPENDIX VII. CONSENT FORM 128/2009

Name of Study: Assessment of sleep disorders in adults with attention-deficit/hyperactivity disorder (ADHD) of the predominantly inattentive (ADHD-I) and combined (ADHD-C) subtypes

Responsible Investigators: Umesh Jain (416) 979-4359
Colin Shapiro (416) 603-5273

Study Contact: Rosalia Yoon (416) 535-8501 ext 4415

You are invited to consider participating in a scientific research study involving adults with attention-deficit/hyperactivity disorder (ADHD) with a sleep complaint. Before you agree to participate in the study, it is important that you understand the purpose, procedures, benefits, discomforts, risks and precautions associated with this study, which are covered in these information sheets. These information sheets may contain words or procedures that you do not understand. If you have any questions about anything in these sheets, please do not hesitate to ask the study investigators or study contact listed above. Please make sure that you understand the study procedures and that all your answers have been answered to your satisfaction before signing the consent form. You should take as much time as you need to make your decision.

Background: A large proportion of subjects with ADHD suffer from sleep disorders that cause difficulties with initiating or maintaining sleep. As a result of these sleep disorders, subjects with ADHD get less sleep than what is necessary and feel sleepy and tired during the day. This is important because getting less sleep can result in ADHD-like symptoms such as inattention, difficulties with learning, and mood problems; or can worsen existing ADHD symptoms. Because of the enormous impact that sleep has on the brain capacities affected in ADHD, scientists have tried, for decades, to investigate the link between ADHD and sleep disorders. However, despite extensive research, the relation between sleep disorders and ADHD is not well understood.

Purpose of the Study: The purpose of this study is to investigate what kinds of sleep disorders occur in ADHD, and how such sleep disorders impact sleepiness, fatigue, and alertness in ADHD.

Overview: As a participant in this study, you will undergo 2 tests to get a complete assessment of your sleep: polysomnography (PSG) and dim light melatonin onset (DLMO) test.

I have read and understood the information on this page: ____________________________ (Subject's Initials)

- PSG is an overnight procedure that records your sleep over a period of two nights to look for any abnormalities in your sleep. 12 thin wires are glued to your face, head, chest and limbs while you sleep at the sleep clinic in a private room. The wires convey information about your sleep to a computer monitored by a sleep technologist, located in another room. There is no pain involved in this procedure as the sticky pads are attached to the skin using paste and skin tape.
- In DLMO test, we measure the secretion of a hormone called melatonin in your saliva. Melatonin is a hormone that your brain releases in the evening, to control what time you go to bed at.

Procedures: The study will take place at the Sleep Research Laboratory at the Toronto Western Hospital. All in all, we will need four visits from you: 1 visit for DLMO testing, 2 visits for PSG, and 1 visit to discuss your results. This amounts to approximately 35 hours of your time distributed throughout 4 visits. The following is an overview of the procedures you will undergo in these four visits:

Visit 1: DLMO testing
- Report to the Sleep Research Laboratory at the Toronto Western Hospital by 7:00 PM.
- Every hour from 8 PM to 3 AM, you will be asked to chew on a cotton ball which absorbs a small amount of saliva and to transfer this cotton ball into a small vial with your tongue.
- Saliva samples will be frozen and sent to a lab for testing.
- There are restrictions associated with this procedure. For DLMO testing we will ask you to:
  - Not brush your teeth immediately before the test and to rinse your mouth with water 15 minutes prior to each saliva collection
  - Not to eat, drink coffee or any coloured beverages, or chew gum. These actions may alter the chemistry of your saliva and interfere with the test
  - Not to eat oats, sweet corn, rice, ginger, tomatoes, bananas, barley and cherries on the day of the test. These foods may contain melatonin or melatonin-like substances that may affect the test.

Visits 2 and 3: PSG testing
- Report to the Sleep Research Laboratory at the Toronto Western Hospital by 9 PM.
- Electrodes are attached to your face, head, chest and limbs by a sleep technologist
- Lights are out at 11 PM, when PSG recordings start. Recordings end at 7 AM the next morning.

Visit 4: Discussion of Results
- Meet with a sleep specialist, Dr Shapiro, to discuss the results of the study.
- During this session, the nature, severity, effects, possible causes, and viable treatment options for your sleep problems and/or sleep disorders will be discussed.

I have read and understood the information on this page: ______________________

(Subject’s Initials)

Confidentiality: Your identity will be kept confidential to the full extent provided by law. In our data collection, you will be identified by an ID # assigned to you as soon as you agree to participate. For research purposes, you will be identified by your ID # only, and research associates will not know any of your personal information other than your date of birth, gender, and ethnicity. The hard copies of the collected data will be stored in a secure, locked storage facility; and the electronic data will be password protected in a locked facility. Data will be kept for up to 7 years, after which all data will be destroyed. Your name or any other personal identifier will not be used in any reports or publications arising from this study. As part of the Research Services Quality Assurance role, studies may be audited by the Manager of Quality Assurance. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and to the extent permitted by law.

Compensation: There is a $10 monetary compensation for participating in this study. If you become ill or are physically injured as a result of participation in this study, medical treatment will be provided. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities.

Risks: DLMO testing has no associated risks. PSG is also a safe procedure. However, you may feel minor psychological or physical discomfort as a result of having multiple wires attached to your body. Moreover, you may experience minor skin irritation due to either the gel or tape used to attach wire electrodes to your body. Skin irritation is only temporary, lasting 2 days at the most. The occurrence of skin irritation is rare and happens in 1-2 per 100 cases.

Benefits: In this study you will receive a clinical assessment of the nature, severity, effects, possible causes, and viable treatment options for your sleep problem or sleep disorder. A direct benefit of participating in this study is that you will receive a complete clinical assessment of your sleep free of charge (DLMO testing costs US$600 per person). On the long run, the information gained in this study could aid in the understanding of neurological mechanisms underlying sleep disorders in ADHD, and thus, could lead to the development of better therapeutic agents for the management of ADHD.

Voluntary Participation: Participation in this study is voluntary. As a result, you may choose to withdraw from the study at any given time. Also, the investigators and staff involved in this study may, at their discretion, end your participation at any time. Your choice to not participate, your choice to withdraw, or your dismissal by us will not affect any treatment needs that you may have at the Centre for Addiction and Mental Health now or in the future.

Additional Information: If you have any questions not answered in these Information Sheets, please do not hesitate to ask. If questions arise in the future, you may contact the study investigators, Dr. Colin Shapiro at (416) 603-5273 or Dr Umesh Jain at (416) 979-4359; or the study contact, Ms Rosalia Yoon at (416) 535-8501 ext 4415.

I have read and understood the information on this page: ____________________________
(Subject’s Initials)

If you suffer any side effects or other injuries during the study, please call the doctors in charge of this study, Dr. Colin Shapiro at (416) 603-5273 or Dr Umesh Jain at (416) 979-4359

If you have any questions regarding your rights as a research subject, you may reach Dr Darby, Chair of the Research Ethics Board at the Centre for Addiction and Mental Health at (416) 535-8501 ext 6876.

AGREEMENT TO PARTICIPATE

I, ___________________________________________, have read (or had read to me) the Information Sheet for the study named “Assessment of sleep disorders in adults with Attention-deficit/hyperactivity disorder (ADHD) of the predominantly inattentive (ADHD-I) and combined (ADHD-C) subtypes”. My role in the study as a research volunteer is to help the investigators collect information about the nature and possible causes of sleep disorders in the ADHD subtypes. This information may or may not be useful in gaining knowledge on the neurobiology of ADHD. My questions, if any, have been answered to my satisfaction. By signing this consent form I do not waive any of my rights. I have been given a copy of this form to keep.

Dr Padraig Dardy, Chair, Research Ethics Board, Centre for Addiction and Mental Health, may be contacted by research subjects to discuss their rights. Dr Dardy may be reached by telephone at (416) 535-8501 ext 6876.

I agree to participate.

Research Volunteer:

Signature: __________________________

Date: __________________________

Name: __________________________ (please print)

Person Obtaining Consent:

Signature: __________________________

Date: __________________________

Name: __________________________ (please print)

I have read and understood the information on this page: __________________________

(Subject’s Initials)
APPENDIX VIII. SUPPLEMENTARY DISCUSSION OF PERSONALITY TRAIT PROFILES IN ADHD

PERSONALITY AND ADHD

Personality is defined as the dynamic organization of psychophysical systems rooted in the reception, processing, and storing of information about experience, that determine an individual’s response to his environment (Allport, 1937; Cloninger et al., 1993). The importance of understanding personality in ADHD is apparent when one considers that ADHD is, among other things, a condition marked by inadequate responses to environmental demands. This raises the possibility that certain personality traits may be causally associated with core symptoms of ADHD and, importantly, that personality traits may be a gateway to understanding ADHD subtype differences.

The Temperament and Character Inventory (TCI) is a multidimensional psychobiological model that explains personality using the product of any factorial combination of four dimensions of temperament – Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence –; and three dimensions of character – Self-Directedness, Cooperativeness and Self-Transcendence (Cloninger et al., 1993). While temperament traits are postulated to have a genetic basis and to be relatively stable throughout life and regardless of mood state (Cloninger, 1987; Cloninger et al., 1991), character traits are self-concepts about goals and values that are strongly influenced by learning and the family environment (Cloninger, 1987).

Persistence is a measure of perseverance despite frustration and fatigue, or the degree to which behaviour is maintained in response to intermittent reward (Cloninger et al., 1993; Kose, 2003). Neurologically, the trait of persistence is believed to be largely influenced by NE, as NE facilitates the acquisition of conditioned signals of reward or relief from punishment and, more specifically, low persistence is postulated to stem from low sensitivity of post-synaptic NE receptors which results in under-activation of NE signaling pathways (Cloninger, 1987; Conners et al., 1999). The finding that persistence was low in my study subjects is not only in line with a previous study of TCI personality traits in ADHD (Faraone et al., 2009), but it also fits into a neurobehavioral model referred to as the Motivational Style Pathway, which proposes that at the core of ADHD pathology are abnormalities in mesolimbic reward circuits associated with a
shortened delayed reward gradient that can lead to repeated failure to effectively respond to tasks related to waiting and delay (Sonuga-Barke, 2002). Importantly, the Motivational Style Pathway does not propose that ADHD is a direct result of abnormal mesolimbic reward circuits, but rather that the core symptoms of ADHD are contextual manifestations of a generalized aversion to delay that develops if the effects of altered reward mechanisms are met with cultural practices such as overtly high standards or intolerance of failure – suggesting that ADHD pathology is a combination of neurological abnormalities and cultural norms or values (Sonuga-Barke, 2002). The incorporation of the role of cultural practices into the construct of ADHD is interesting in the context of the TCI because character traits are influenced by learning and the family environment and, as such, it would be expected that some character traits would be affected in ADHD, specifically if such character traits are associated with aversion to delay. Among the character dimensions of the TCI, self-directedness appears to be of most relevance to ADHD.

Self-directedness is a character trait that refers to “willpower”, or the ability to control, regulate, and adapt behaviour to individual chosen goals and values (Cloninger, 1993). This trait has been reported to be associated with delay discounting (the preference for smaller immediate rewards over larger but delayed rewards) (Anokhin et al., 2011) and, in line with descriptions of ADHD (Pennington & Ozonoff, 1996; Barkley, 1997; Schachar et al., 2000; Castellanos & Tannock, 2002), those low in self-directedness have been described as “…seemingly lacking in an internal organizational principle that results in an inability to define, set and pursue meaningful goals…” (Cloninger, 1993). In concordance with previous studies (Faraone et al., 2009; Cho et al., 2009), self-directedness was very low in the ADHD subjects in this study. Within the context of the Motivational Style Pathway, I speculate that this very low self-directedness is highly associated with the aversion to delay that develops in subjects with ADHD when abnormalities in the mesolimbic reward system associated with low persistence are met with negatively moderating cultural and environmental effects and, thus, I speculate that low self-directedness is a precursor to the core symptoms of ADHD.
**ADHD subtype differences in personality traits**

Previous studies have reported that novelty seeking and harm avoidance scores are higher in ADHD subjects than in healthy controls (Downey et al., 1996; 1997; Pennington & Ozonoff, 1996; Anckarsater et al., 2006; Jacob et al., 2007; Faraone et al., 2009) and, indeed, the subjects of this study were found to have high scores on both dimensions (Table 3.1). The results of this study, however, also suggest that in addition to ADHD-control differences, there are ADHD subtype differences, as novelty seeking and self-transcendence scores were significantly higher for ADHD-C subjects, and harm avoidance scores were significantly higher for ADHD-I subjects.

**Novelty Seeking Behaviour**

Novelty seeking behaviour is a dimension within the behavioural activation system, which is a system that regulates behaviour in response to signals of reward or relief from punishment (Cloninger, 1987; Becerra-Garcia, 2010). While the neurological mechanisms underlying novelty seeking are not well understood, it appears to involve dopamine signaling: genetic studies have shown associations between experience seeking behaviour and polymorphisms in the DRD4 and catechol-O-methyl transferase (COMT) genes (Benjamin et al., 1996; Ebstein et al., 1996; Reuter & Hennig, 2005; Martin et al., 2007) and, more recently, neuroimaging studies indicate that high novelty seeking is associated with reduced D2 receptor activity in the substantia nigra SN/VTA (Zald et al., 2008; Tournier et al., 2013). Importantly, D2 receptors in the midbrain provide potent inhibition of DA release (Mercuri et al., 1997; Zald et al., 2008) and, thus, reduced D2 receptor activity in the SN/VTA could significantly affect neurological functions regulated by the mesolimbic, mesocortical, and nigrostriatal pathways, since these pathways originate from dopaminergic neurons within the SN/VTA (Haber & Knutson, 2010; Krebs, 2011). This is important within the context of ADHD because the involvement of these pathways in the pathology of ADHD has been reported. In addition to the proposed role of mesolimbic reward systems in the Motivational Style Pathway, one of the most widely recognized constructs of ADHD proposes a role of mesocortical pathways in the pathology of ADHD. According to this model – known as the Dysregulation of Thought and Action Pathway – at the core of ADHD pathology are abnormalities in mesocortical control circuits that lead to
deficits in response inhibition that manifest cognitively in the form of poor task engagement and behaviourally in the form of ADHD symptoms (Sonuga-Barke, 2002). While the Motivational Style Pathway and the Dysregulation of Thought and Action Pathway are fundamentally different constructs of ADHD, Sonuga-Barke has proposed a dual pathway model of ADHD in which the two constructs are combined such that abnormalities in both the mesolimbic and mesocortical dopamine pathways lead to ADHD pathology (Figure 0.1).

**Figure 0.1 The dual pathway model of ADHD.**
The dual pathway model of ADHD, proposed by Sonuga-Barke (2002), views ADHD as a composite of two previously existing models of ADHD: the disregulation of thought and action pathway model, which proposes that cognitive and behavioural deficits in ADHD stem from abnormal regulation of inhibitory function by meso-cortical control circuits; and the motivational style pathway, which proposes that ADHD symptoms are contextual manifestations of a generalized aversion to delay that develops when behavioural abnormalities associated with a shortened delay reward gradient are met with intolerant cultural norms or values. Figure adapted from Sonuga-Barke, 2002.
The finding that novelty seeking behaviour was significantly higher for the ADHD-C than for the ADHD-I subjects (Table 3.1), however, is difficult to interpret within the context of the Dual Pathway Model of ADHD. This is because the Dual Pathway Model does not differentiate between ADHD subtypes, as it is a construct based on the ADHD-C subtype (Sonuga-Barke, 2002), and to the best of my knowledge, not much is known or speculated about the neurological mechanisms underlying the ADHD-I phenotype. Nevertheless, given the similarities between ADHD subtypes (e.g. low persistence, very low self-directedness, inattention), it is likely that mesocortical and mesolimbic pathways are affected in similar ways in Inattentive and Combined subtypes, such that the Dual Pathway Model of ADHD applies to both ADHD subtypes. Importantly, it is possible that what differentiates the Inattentive from the Combined subtype is that the ADHD-I subtype is associated with an additional component that alters the neuromodulation of personality traits and the core symptoms of ADHD that gives rise to the ADHD-I phenotype. This possibility is discussed in the next section.

Harm Avoidance

Indirect evidence for an additional pathway associated with the Inattentive subtype comes from the finding that harm avoidance was very high for ADHD-I subjects but variable for ADHD-C subjects. Harm avoidance is a measure of sensitivity to aversive and novel stimuli that evoke negative emotions (Cloninger, 1986). Initially thought to be associated with serotonergic neurotransmission (Cloninger, 1986; 1987), regulation of harm avoidance was postulated to occur via serotonergic neurons that project from the raphe nuclei to the limbic system to interrupt behaviour when the unexpected is encountered (Warburton, 1977; Cloninger, 1987; Gray, 1982; 1983), and from the dorsal raphe nuclei to the dopaminergic neurons in the substantia nigra to inhibit activity in response to signals of punishment or non-reward (Thiebot et al., 1984). However, more recent studies have failed to provide consistent evidence on the involvement of serotonin, suggesting that neurotransmitter systems other than serotonin are associated with harm avoidance (Tuominen et al., 2012).

Anatomically, harm avoidance appears to be associated with a high degree of intrinsic connectivity between the anterior insula and the anterior cingulate cortex (ACC), and between the anterior insula with the dorsolateral PFC (Markett et al., 2013). While the literature on the
neurotransmitter systems associated with the neuromodulation of harm avoidance in these brain regions is not abundant, recent studies report that harm avoidance scores correlate positively with the availability of µ-opioid receptors in the ACC, the ventromedial and dorsolateral PFC, and the right anterior insula – a finding that was proposed to be tantamount to low opioid drive in these areas (Tuominen et al., 2012). Harm avoidance has also been reported to be negatively associated with 5-HT(1A) receptor binding potential in the amygdala, ACC, and insular cortex (Hillert et al., 2013). These areas of the brain are involved in the regulation of amygdala responses to threat and fearful stimuli (Phelps et al., 2004; Etkin et al., 2006; Urry et al., 2006; Tuominen et al., 2012) as well as the identification of emotionally significant stimuli and appraisal of threat (Simmons et al., 2006; Mechias et al., 2010; Tuominen et al., 2012) and it is postulated that trait harm avoidance in anxiety disorders is associated with overactivity in these areas (Sylverster et al., 2012).

Within the context of ADHD, the significantly higher scores of harm avoidance in Inattentive subjects suggest that neurological mechanisms underlying this subtype may include overactivity in brain networks involved in the modulation of responses to threat as well as fearful and emotionally significant stimuli, possibly as a result of low opioid drive and abnormal serotonergic transmission in these brain regions. Importantly, given that harm avoidance is associated with inhibition of response, it is likely that the overactivity of brain networks associated with harm avoidance impinge on the neuromodulation of other behaviours. Within the context of the TCI, one of the behaviours that may be negatively affected may be that of novelty seeking. Sensation seeking is a personality trait related to novelty seeking behaviour that includes components such as sensation, thrill, and adventure seeking, disinhibition, and susceptibility to boredom (Zuckerman, 1994; 2005; Joseph et al., 2009). While direct evidence on an opposing effect of harm avoidance on novelty seeking behaviour is lacking, studies on the neurobiology of sensation seeking have reported that one of the key differences between high sensation seekers and low sensation seekers is that low sensation seekers exhibit stronger cortical inhibition (Zuckerman, 1994; 2005; Joseph et al., 2009). Also, low sensation seekers exhibit stronger and earlier activation in the ACC and anterior medial orbitofrontal cortex in response to high-arousal stimuli (Zuckerman, 2005; Joseph et al., 2009). These observations suggest a neurological association between sensation seeking and harm avoidance.
Self-Transcendence

Self-transcendence is the concept of the self as part of the universe that is related to the acceptance, identification, or spiritual union with nature and its source (Cloninger et al., 1993; Kose, 2003). Self-transcendence differed significantly between ADHD subtypes – it was very low for the majority of ADHD-I subjects but variable in ADHD-C, with half of the ADHD-C subjects ranking between the 10th and 65th percentiles. Although the reasons why self-transcendence is lower in ADHD-I than in ADHD-C are not well understood, I speculate that it may stem from high harm avoidance in ADHD-I subjects, as high scores in harm avoidance subscales such as fear of uncertainty and anticipatory worry may negatively impact facets of self-transcendence such as self-consciousness and transpersonal identification.

Conclusion

My findings suggest that high harm avoidance and low self-transcendence are part of the ADHD-I phenotype; and that high novelty seeking, hyperactivity/restlessness, and impulsivity are part of the ADHD-C phenotype.

I propose that ADHD pathology is associated with abnormalities in mesolimbic reward circuits that lead to low persistence, which in combination with the moderating role of cultural practices, lead to the gradual development of aversion to delay and low self-directedness that, in turn, manifests contextually in the form of inattention/memory problems and impulsivity/emotional lability. Of note, it has also been hypothesized that mesolimbic abnormalities in ADHD are underlain by a DA deficiency in brain reward centres that leads to feelings of discomfort and a need for reinforcers to elevate DA levels back to normal (Blum et al., 1996; 2008; Volkow et al., 1997). Importantly, since novel stimuli and natural reinforcers such as food and sex lead to phasic release of DA from the VTA (Probst & van Eimeren, 2013), I propose that novelty seeking, hyperactivity, and impulsivity are reward-directed behaviours under the regulation of the BAS that ADHD-C subjects engage in to correct a DA deficiency. While the secretion of DA is normally modulated by presynaptic D2 receptors, low basal levels of extracellular DA in subjects with DA deficiency leads to underactivation of presynaptic D2 receptors and, thus, poor regulation of DA secretion. As a result, I speculate that activation of the BAS in subjects with
DA deficiency results in phasic overshoot of DA, and subsequent overactivation of dopamine signaling in the striatum, which manifests in the form of hyperactivity and impulsivity in ADHD. Importantly, reward-directed behaviour in the healthy brain is adaptively regulated by the PFC, which inhibits contextually inappropriate behaviours. PFC function, however, may be compromised in ADHD as a result of abnormalities in mesocortical signaling pathways and, thus, the manifestation of ADHD symptoms may be further enhanced by deficits in response inhibition, leading to the high scores of novelty seeking behaviour, hyperactivity, and impulsivity in ADHD-C. I hypothesize that the overactivity of neurophysiologic processes proposed in ADHD-C (Mayes et al., 2009) stems from high activation of reward-directed behaviours.

While the activation of behaviours in response to cues of reward is important, learning to avoid potential harm is also essential for survival, and the reward system is opposed by the punishment system, which mediates inhibition of behaviour in order to avoid punishment (Palminteri et al., 2012). The reward system and punishment system are believed to be subserved by different areas of the brain: the reward system is believed to be regulated by the ventral striatum, OFC, ACC, amygdala, and hippocampus (Probst & Eimeren, 2013); and the punishment system is believed to be regulated by the anterior insula (Palminteri et al., 2012).

ADHD-I may be associated with overactivation of brain networks associated with punishment-based learning. This is evidenced by the finding that HA – which has also been reported to involve the anterior insula (Markett et al., 2013) – was significantly higher in ADHD-I than in ADHD-C subjects. The importance of this is that overactivity of brain networks associated with inhibition of response may impinge on the neuromodulation of reward-directed behaviours, leading to inhibition of behaviors such as hyperactivity, impulsivity, and novelty seeking. In this respect, I propose that while, similar to the case with ADHD-C, the ADHD-I phenotype is underlain by abnormal regulation of mesolimbic and mesocortical signaling pathways associated with low attention, low persistence, and low self-directedness; execution of reward-directed behaviours such as novelty seeking, hyperactivity, and impulsivity in response to DA deficiency is inhibited by overactive brain networks associated with punishment in ADHD-I subjects, resulting in the lower scores on novelty seeking, hyperactivity, and impulsivity. Moreover, since stronger activation of the ACC in low sensation seekers is associated with stronger cortical
inhibition, I propose that neurophysiologic underarousal proposed in ADHD-I (Mayes et al., 2009) stems from overactivity of brain networks associated with punishment.

**Appendix References**


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