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Sleep spindle activity in children with ADHD

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Sleep spindle activity in children with ADHD

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RÉSUMÉ

Le trouble du déficit de l'attention/hyperactivité (TDA/H) est le désordre du comportement le plus commun chez les enfants. Les études suggèrent qu'un pourcentage élevé d'enfants atteints de TDA/H souffre de problèmes de sommeil et de somnolence diurne. Le mécanisme sous-jacent à ces difficultés demeure inconnu. Plusieurs études ont suggéré que les fuseaux de sommeil jouent un rôle dans les mécanismes de protection du sommeil. L'objectif de cette étude est de comparer les fuseaux lents (11-13 Hz) et rapides (14-15 Hz) chez des enfants atteints du TDA/H et des sujets contrôles. Nous prévoyons que comparativement aux enfants contrôles, les enfants atteints du TDA/H montreront une plus faible densité des fuseaux lents et rapides, et auront des fuseaux plus courts (sec), moins amples (uV) et plus rapides (cycle/sec). Enfin, nous prévoyons que ces effets seront plus prononcés dans les dérivations cérébrales antérieures que dans les dérivations plus postérieures du cerveau.

Les enregistrements polysomnographiques (PSG) du sommeil de nuit ont été menés chez 18 enfants diagnostiqués avec le TDA/H et chez 26 sujets témoins âgés entre 7 et 11 ans. Un algorithme automatique a permis de détecter les fuseaux lents et rapides sur les dérivations frontales, centrales, pariétales et occipitales. Les résultats ont montré que, les caractéristiques PSG du sommeil ne différaient pas significativement entre les deux groupes. On ne note aucune différence significative entre les groupes sur nombre/densité des fuseaux lents et rapides ainsi que sur leurs caractéristiques respectives.

Cette étude suggère que les mécanismes de synchronisation du l'EEG en sommeil lent, tel que mesuré par la densité et les caractéristiques des fuseaux lents et rapides en sommeil lent ne différent pas chez les enfants atteints du TDA/H.

Mots clés: TDA/H, fuseaux de sommeil, sommeil, enfant.

RÉSUMÉ

Attention Deficit Hyperactivity Disorder (ADHD) is a commonly diagnosed behavioural disorder in children. Evidence suggests that a high proportion of children with ADHD suffer from sleep difficulties and daytime sleepiness. However, the mechanism underlying this deficit in alertness is unknown. Various studies suggest that sleep spindles inhibit arousing sensory input and help preserve sleep. The objective of this study was to compare slow (11-13 Hz) and fast (14-15 Hz) spindle activity between children with ADHD and controls. We expected that compared to controls, children with ADHD would show a lower density (number of spindles per minute of NREM sleep) of slow and fast spindles. We also predicted that children with ADHD will have shorter (sec) fast and slow spindles, lower amplitude (uV) and faster frequency (Hz) than controls. Finally, we expected these effects would be more pronounced in the frontal rather than more posterior derivations of the brain.

Overnight sleep recordings were conducted in 18 children diagnosed with ADHD without comorbid psychiatric problems and in 26 healthy controls. The subjects' ages ranged from 7 to 11 years. An automatic algorithm detected the slow and fast spindles on the frontal, central, parietal and occipital derivations. The results showed that children with ADHD had similar PSG sleep architecture (sleep efficiency, stages of sleep) compared to controls. Sleep spindle activity did not significantly differ between the two groups in terms of number, density, amplitude and length.

This study suggests that mechanisms of sleep EEG synchronization, as expressed by the number and density of sleep spindles presently identified in the ongoing EEG, do not differ between children with ADHD and controls.

Key words: ADHD, Sleep spindles, sleep, children

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LISTE DES ABBREVIATIONS

ADHD: Attention Deficit Hyperactive Disorder

DRD4 allele: Dopamine 4 Receptor Subtype

DAT: Dopamine Transporter

MZ: Monozygotic

DZ: Dizygotic

PSG: Polysomnography

REM: Rapid Eye Movement

NREM: Non-Rapid Eye Movement

SWS: Slow-Wave Sleep

GABA: γ-Aminoburyric Acid

IPSPs: Inhibitory Postsynaptic Potentials

EPSPs: Excitatory Postsynaptic Potentials

IQ: Intelligent Quotient

FSIQ: Full Scale IQ

PIQ: Performance IQ

VIQ: Verbal IQ

CNS: Central Nervous Systems

MPH: Methylphenidate

DSM-IV: Diagnostic and Statistical Manual, 4th edition

DISC-IV: Diagnostic Interview Schedule for Children

CBCL: Conner's Behavior Checklist

CGI-T: Conner's Global Index for Teacher

CGI-P: Conner's Global Index for Parents

WISC-IV: Wechsler Intelligence Scale for Children-IV

EOG: Electrooculography

EMG: Electromyography

RMS: Root Mean Square

ANOVA: One-way Analysis Of Variance

ANCOVA: Analyses Of Covariance

SES: Socioeconomic Status

Je dédie ce mémoire de maitrise à ma mère et

à mon père qui m'ont appris la persévérance

et la rigueur dans tout ce que j'entreprends.

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1. OVERVIEW AND OBJECTIVES

Attention deficit/hyperactivity disorder (ADHD) is characterized by high levels of inattention and/or impulsivity/hyperactivity. Although children with ADHD show signs of hyperactivity, they also suffer from significant daytime sleepiness (Golan, Shahar, Ravid, & Pillar, 2004) and underarousal of the cortex or other sections of the central nervous system (CNS) (Sergeant, 2005; Zentall & Zentall, 1983). However, the mechanism underlying this deficit in alertness is not known.

One hypothesis proposed to explain the low level of arousal in children with ADHD is that a deficit in sleep impairs their daytime arousal. Several studies using traditional EEG have been conducted with children diagnosed with ADHD (Gruber et al., 2009; Kirov et al., 2004; Lecendreux, Konofal, Bouvard, Falissard, & Mouren-Simeoni, 2000). These studies have mainly focused on sleep macrostructures, i.e., percentage of REM sleep, sleep efficiency, total sleep time. The results yielded from these studies have been inconsistent.

Sleep spindles indicate the onset of human stage 2 sleep. They function to inhibit arousing sensory input and to preserve sleep (Steriade & Timofeev, 2003; Yamadori, 1971). Their appearance in the EEG is a sign that sleep has taken over wakefulness (Rechtschaffen & Kales, 1968). The present study sought to examine the hypothesis that a deficit in sleep spindle activity underlies the hypoaroused state in children with ADHD.

The goal of the present study was to compare sleep spindle activity between children with ADHD and controls. In order to review relevant data and to better address the rationale of the present study, this thesis first presents research on sleep disturbances in ADHD individuals. Next, the potential relevance of sleep spindles to

the underlying pathophysiology of this disorder will be discussed. Finally, this study pertaining to the comparison of sleep spindles in children with ADHD and controls will be presented and discussed.

1.1 Attention Deficit Hyperactivity Disorder (ADHD)

1.1.1 Diagnosis and symptoms

ADHD is one of the most prevalent psychiatric disorders in children. In the United States, 3% to 7% of school-aged children are affected (American Psychiatric Association, 2000), and is two times more prevalent in boys than in girls (Centers for Disease Control and Prevention, 2010). It is generally characterized by inappropriate overactivity, distractibility, inattention and impulsive behaviour across multiple settings (American Psychiatric Association, 2000). Based on the number of symptoms in each syndrome cluster (Inattention/ Hyperactive-Impulsive) that a child exhibits, three types of ADHD have been defined (See Annex 1 for complete diagnostic criteria) (American Psychiatric Association, 2000). Symptoms must have persisted for at least six months to a degree that is maladaptive and inconsistent with the child's developmental level. The diagnostic criteria also require that the hyperactive-impulsive or inattentive symptoms have caused impairments in two or more settings, such as at school and at home, and the onset of the behavioural symptoms must have occurred before the age of seven. In addition, these symptoms should not be caused by other psychiatric disorders.

Structured interviews along with questionnaires are essential for the diagnosis of ADHD. A thorough evaluation by a clinician should be multi-dimensional.

Preferably, this entails an interview with the parents or caretaker, an examination of the child's mental and physical health, a cognitive assessment, and the analysis of ADHD-focused rating scales and school reports (American Academy of Pediatrics Committee on Quality Improvement, 2000; Goldman, Genel, Bezman, & Slanetz, 1998).

Children with ADHD exhibit impairments in executive functions, attention, impulse control, and activity regulation. Such impairments cause other problems in task organization, learning, and decision making that may occur in academic or social environments (Barkley, 1998). These symptoms persist into adulthood in 40% to 60% of individuals (Barkley, Fischer, Smallish, & Fletcher, 2002; Fischer, Barkley, Smallish, & Fletcher, 2005). By the time they reach adolescence and late adulthood, many patients will display an established pattern of academic, familial, and social dysfunction (Johnston, 1998).

Studies have shown that having a diagnosis of ADHD increases the frequency of other comorbid disorders (Angold, Costello, & Erkanli, 1999; Austin, Reiss, & Burgdorf, 2007; R. Tannock, 1998), including conduct disorder, oppositional defiant disorder, as well as mood and affective disorders (Bauermeister et al., 2007). About one fifth of children with ADHD also have associated learning disorders (Karande, 2005). As a result, this disorder is highly comorbid with other psychiatric and developmental disorders which makes it more complex and difficult to determine a clear etiology and optimal treatment.

1.1.2 Etiology

ADHD is a multifaceted and heterogeneous disorder. It is well established that there is a heritable component to this disorder: twin studies have shown that the rate of concordance is significantly higher among monozygotic (MZ) twins than in same-sex dizygotic (DZ) twins. (Levy, Hay, McStephen, Wood, & Waldman, 1997; Levy, McStephen, & Hay, 2001; Sherman, McGrue, & Iacono, 1997; E. G. Willcutt, Pennington, & DeFries, 2000). However, the fact that the MZ concordance is less than 100% suggests that other factors also play a causal role in the pathogenesis of ADHD (Biederman et al., 1992; Bradley & Golden, 2001; Faraone et al., 1993; Thapar, Holmes, Poulton, & Harrington, 1999) These factors, detailed below, include catecholaminergic systems, brain mechanisms and environmental factors.

a) Catecholaminergic Systems

The dopaminergic and noradrenergic systems have modulatory influences on working memory and attention functions in the prefrontal cortex (Arnsten, 1997). Two related neurotransmitters in the pathophysiology of ADHD are dopamine (DA) and norepinephrine (NE). Dopamine plays an important role in the function of the prefrontal-subcortical system, and is critical in the regulation of learning, working memory, as well as maintaining trained or conditioned responses and motivated behaviours (Goldman-Rakic, 1994; Moore & Bloom, 1978). Norepinephrine is involved in maintaining alertness and attention (Arnsten & Li, 2005).

The two catecholaminergic systems appear to be impaired in children with ADHD who have difficulty regulating their own level of alertness and awareness of important stimuli (Arnsten, 1997). For example, imaging studies have provided evidence of decreased DA release (Volkow et al., 2007) and increased DAT binding

(Spencer et al., 2007) in the striatum of adults with ADHD. It is likely that this reflects global reductions of DA release throughout the brain, as earlier studies have suggested reduced catecholamine levels in the PFC as well (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998). In one animal study, reduced DA in the PFC produced locomotor hyperactivity (Simon, 1981). These findings are all consistent with the loss of catecholamines in the PFC being most responsible for ADHD symptoms.

Another approach suggests a deficiency in the dopamine receptor D4 (DRD4) gene and over-expression of dopamine transporter-1 (DAT1) (Coghill & Banaschewski, 2009) in individuals with ADHD. The DRD4 receptor uses DA and NE to modulate attention and responses to one's environment (Langley et al., 2004). The DAT1 protein reuptakes DA/NE into the presynaptic nerve terminal, thereby limiting the duration of action of the neurotransmitters on the postsynaptic receptors (Arnsten, 2000).

The aforementioned defects in catecholamine neurotransmission likely explain why dopamine agonists, such as methylphenidate (MPH), which has been shown to modulate neuronal activity in the striatum during stimulus-controlled tasks involving motor inhibition (Vaidya et al., 1998), have clinical benefits when used to treat ADHD children. For example, poor performance by children with ADHD in the Continuous Performance Task (CPT) has been shown to be improved with an acute dose of MPH (Konrad, Guenther, Hanisch, & Herpertz-Dahlmann, 2004; Riccio, Reynolds, & Lowe, 2001; Solanto, 1998).

It is unlikely that a single gene will be linked to ADHD; rather, ADHD may be due to the interaction of several genes involved in the functions of different neurotransmitters. Several studies suggest that the serotoninergic pathway may also be involved in the response to psychostimulants. In particular, the serotonin transporter (SERT) has been examined as a potential causal factor in ADHD. SERT is a solute carrier protein responsible for the reuptake of serotonin from the synaptic gap back to the pre-synaptic neuron (Müller et al., 2008). Reduced central serotonergic activity has been implicated in poor impulse regulation and aggressive behaviour in animals, adults and also young children (Halperin et al., 1997). The actions of the neurotransmitter serotonin are terminated by reuptake via a sodium-dependent serotonin transporter. The 44-bp insertion/deletion in the promoter region of SERT (SERTPR) has been reported to be positively associated with ADHD (Curran, Purcell, Craig, Asherson, & Sham, 2005; Kent et al., 2002).

b) Brain Function/Mechanisms

Several types of studies provide information about the locus of ADHD's pathophysiology in the brain. Neuro-imaging studies suggest that malfunction of the fronto-subcortical pathways is related to core ADHD symptoms (Biederman, 2005). Brain alterations observed in ADHD include significantly smaller volumes in the dorsolateral prefrontal cortex, caudate, pallidum, corpus callosum, and cerebellum (Seidman, Valera, & Makris, 2005). Specifically, the prefrontal cortex (PFC) is particularly related to ADHD. Studies using structural brain imaging indicate that individuals with ADHD often have smaller PFC volume, particularly on the right side of the brain (Casey et al., 1997; Castellanos et al., 1996).

The prefrontal cortex is responsible for memory, concentration and strategic planning, with the right hemisphere specialized for behavioral inhibition. These brain functions represent the same core deficits exhibited by children with ADHD. For example, Castellanos *et al.* (2001) found that smaller total cerebral volume was associated with greater attention problems. Specifically, right frontal volume reductions were reported to correlate significantly with poorer performance on response inhibition tasks (Casey, et al., 1997) and on sustained attention tasks (Semrud-Clikeman et al., 2000), both of which are known to be impaired in ADHD (R. Tannock, Martinussen, & Frijters, 2000; E. Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

First-line treatments for ADHD include stimulant medications such as methylphenidate, which block the reuptake of DA and NE into the presynaptic neuron and increasing their availability in the PFC (Biederman & Spencer, 1999). This supports the hypothesis that one mechanism by which stimulant medications produce positive effects on ADHD symptoms is through the increase in dopaminergic and noradrenergic activity in the PFC.

c) Environmental Factors associated with ADHD

Several studies having included clinic-referred participants have shown that prenatal or perinatal complications have a small but significant association with ADHD (Breslau et al., 1996; Milberger, Biederman, Faraone, Guite, & Tsuang, 1997). Complications include low birth weight (Breslau, et al., 1996), fetal distress (Hartsough & Lambert, 1985), prenatal exposure to alcohol (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002) or tobacco (Milberger, Biederman, Faraone,

Chen, & Jones, 1996; Milberger, et al., 1997), and family problems during pregnancy (Milberger, et al., 1997). These reported pre/perinatal factors may act in an additive or interactive approach with the genetic influences to increase risk for ADHD, or may even represent a different etiological (i.e., non-genetic) pathway that is sufficient to cause the later development of ADHD in some cases (Swanson et al., 2000).

1.1.3 Hypoarousal theory regarding children with ADHD

Several models have suggested that children with ADHD suffer from under-arousal in the cortex or other components of the central nervous system (CNS) (Statterfield, 1975; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005; Zentall & Zentall, 1983). The hypoarousal theory suggests that the hyperactivity and impulsivity of children with ADHD are the results of having non-optimal arousal levels. This results in impaired functioning and consequently, the excessive motor activity may be a compensatory mechanism that helps them to stay awake and alert (Weinberg & Harper, 1993). This suggests that motor hyperactivity may be considered as a reaction to the hypoaroused condition needed to counteract somnolence (Lecendreux, et al., 2000). Moreover, impulsivity may be related to a decreased ability to control behavior due to fatigue, since children with ADHD are significantly sleepier during the day, compared with control children (Lecendreux, et al., 2000).

EEG studies of children with ADHD have generally found an increase in theta activity, primarily in the frontal areas, decreased alpha and beta activity, and an increase in the theta/alpha and theta/beta ratios compared to normal children. Such EEG patterns are also found in individuals who suffer from insufficient sleep

(Ferreira et al., 2006). One study found that sustained wakefulness and sleep deprivation cause similarly increased theta and decreased alpha activities in normal participants, suggesting that insufficient sleep is associated with daytime hypoarousal (Boonstra, Stins, Daffertshofer, & Beek, 2007). However, despite the fact that abnormalities related to sleep and alertness have been hypothesized (Douglas, 1985), the mechanisms underlying daytime sleepiness and the hypoaroused state in children with ADHD, as well as its relation to sleep patterns remain unknown.

1.2 Sleep

In humans, sleep is divided into two states: rapid eye movement (REM) and non-rapid eye movement sleep (NREM; stages 1, 2, 3 and 4). Each has a different set of physiological, neurological and psychological features. During the night, the NREM and REM stages alternate and the complete cycle usually takes about 90 minutes.

Stage 1, which accounts for 5% of the total sleep time, generally occurs 5-10 minutes after bed time and lasts only few minutes upon falling asleep and is the lightest stage of sleep. It is also considered as a transition between wakefulness and sleep. Stage 1 EEG rhythm changes from alpha waves, which have a frequency of 8 to 13 Hz, (common in the awaking state) to theta waves (frequency of 4 to 7 Hz). Stage 2 is slightly more synchronized and occurs 10 to 20 minutes after sleep onset and accounts for 50% of the total sleep time. This stage features sleep spindles, which are intermittent 12 to 15 Hz oscillations and K complexes, which are high-amplitude sharp waves. Next follows stages 3 and 4, which collectively are considered as slow-

wave sleep (SWS) which account for 25-30 % of the total sleep time in children. In stage 3, EEG begins with large amplitude and slow delta (1 to 4 Hz) rhythms. Stage 4 has the same attributes as stage 3, but with large EEG rhythms frequencies up to 2 Hz and amplitudes greater than 75 μV (Harris, 2005). REM sleep in adult humans usually occurs 90-120 minutes after falling asleep and accounts for 20-25% of the total sleep time. The EEG waves in REM are small and irregular, with big and sudden bursts of eye activity. The brain wave activity at this time resembles wakefulness more than sleep, and is accompanied by vividly recalled dreams (Cameron, 2005).

Sleep of children also differs from adults in various ways. Sleep duration decreases with age, as children require more sleep than adults. In contrast, sleep latency, percentages of stage 1 and stage 2 sleep increases with age while percentage of REM sleep decreases. In addition, sleep cycles last for about 50 minutes in children and 90 -110 minutes in adults. Children's cycles contain a relatively large amount of slow-wave (stage 3 and 4) sleep, whereas slow-wave sleep in elderly adults is relatively shorter and fewer.

1.3 Sleep in children with ADHD

Fifty to seventy-five percent of children with ADHD seen in clinical practice are reported to suffer from chronic sleep difficulties, including difficulties in initiating and maintaining sleep, frequent awakenings and higher incidences of restless sleep (Ball, Tiernan, Janusz, & Furr, 1997; Cohen-Zion & Ancoli-Israel, 2004; Corkum, Tannock, & Moldofsky, 1998; Owens, 2005). Both objective and subjective measures have been used to study the nature of sleep problems in children with ADHD.

1.3.1 Sleep and ADHD – Findings Based on Subjective measures

Subjective studies have used sleep questionnaires filled out by the parents/primary caregivers or, less frequently, by the children/adolescents themselves. Subjective parent reports consistently indicate sleep problems in children with ADHD, with prevalence rates and levels of intensity generally two or three times higher than in controls (Owens et al., 2009). The reported problems include bedtime resistance (Corkum, Tannock, Moldofsky, Hogg-Johnson, & Humphries, 2001; Owens, Maxim, Nobile, McGuinn, & Msall, 2000), delayed sleep onset (Stein, 1999; Trommer, Hoeppner, Rosenberg, Armstrong, & Rothstein, 1988), frequent night awakenings (Ball, et al., 1997; Kaplan, McNicol, Conte, & Moghadam, 1987; Trommer, et al., 1988), frequent motor movements during sleep (Busby, Firestone, & Pivik, 1981; Corkum, et al., 1998), and daytime sleepiness (LeBourgeois, Avis, Mixon, Olmi, & Harsh, 2004; Marcotte et al., 1998; Trommer, et al., 1988).

1.3.2 Objective measures

Objective studies have used multi-channel polysomnography (PSG), actigraphy, (a wristwatch-like device that measures sleep/wake periods) or the gold standard to measure daytime fatigue: Multiple Sleep Latency Test (MSLT), which physiologically measures sleep latency at different times of the day. The test is based on the idea that the more tired the subjects are, the faster they will fall asleep. In contrast to the consistent finding from subjectively measured nocturnal sleep parameters, results from objective studies are less consistent.

a) Findings Based on PSG Studies

A few PSG studies have documented differences in the macrostructure of sleep, such as sleep efficiency and sleep stage differences, but these findings are not consistent. For example, studies found changes in REM sleep in ADHD children compared to controls, such as longer REM latency (Busby, et al., 1981), shorter REM sleep latency (Khan, 1982), a decreased overall REM sleep (Greenhill, Puig-Antich, Goetz, Hanlon, & Davies, 1983), such as shorter duration of REM sleep and smaller percentage of total sleep time spent in REM sleep (Gruber, et al., 2009). A significantly higher number of sleep cycles (Kirov, et al., 2004) and shorter sleep durations (Gruber, et al., 2009; Owens, et al., 2009) in children with ADHD compared to healthy controls have also been reported. One recent study (Silvestri et al., 2009) showed differences in almost all sleep variables investigated. In comparison to controls, children with ADHD had a lower percentage of REM sleep, more percentage of stage 2 and 3, lower sleep efficiency %, larger arousal index, shorter total sleep time and longer REM latency. On the other hand, several studies found that children with ADHD show no sleep architecture abnormalities on PSG recordings when compared with controls (Konofal, Lecendreux, Bouvard, & Mouren-Simeoni, 2001; Lecendreux, et al., 2000).

b) Findings Based on Actigraphys

More recently, actigraphy based studies have shown that children with ADHD have unstable sleep patterns (Gruber & Sadeh, 2004; Gruber, Sadeh, & Raviv, 2000) when compared with controls, including increased instability in sleep onset, shorter sleep duration, less actual sleep time, and significantly higher levels of nocturnal activity (Konofal, et al., 2001). Overall, although results from PSG studies are

inconsistent, actigraphy studies suggest more motor activity and fragmented sleep in children with ADHD (Cortese, Faraone, Konofal, & Lecendreux, 2009). Results from studies using video analysis are consistent with actigraphy findings, indicating that children diagnosed with ADHD have higher levels of nocturnal activity than controls (Busby, et al., 1981; Corkum, et al., 1998; Konofal, et al., 2001).

c) Finding Based on MSLT Studies

It has been suggested that fatigue in children may manifest itself in behaviours such as hyperactivity and inattention. This is in contrast to fatigue experienced in adults who demonstrate inactivity and lethargy (R. D. Chervin, Dillon, Bassetti, Ganoczy, & Pituch, 1997; Dahl, Holttum, & Trubnick, 1994). Therefore, it is possible that children with ADHD are tired and hypoaroused rather than energetic and alert during the day. Such behavioural manifestation of fatigue makes it difficult to determine the fatigue level of children by observation or using subjective reports. Hence, the use of objective measures to assess fatigue is necessary with children.

Results of studies that have used MSLT, consistently show that children with ADHD show excessive physiological fatigue as indicated in the fact that they fall asleep faster during the in MSLT compared to control children (Golan, et al., 2004; Lecendreux, et al., 2000). Studies using waking EEGs also confirmed that excess theta pattern, which indicates “sleepiness”, is a common pattern seen in children with ADHD (Snyder & Hall, 2006). Therefore, these findings suggest the existence of a deficit in the control of arousal, and these children are actually sleepy compared to children without ADHD.

The controversy regarding PSG sleep abnormalities in children with ADHD, combined with the findings suggesting that children with ADHD are sleepy, opens the question as to the mechanism underlying the association between sleep, sleepiness and ADHD. EEG studies in children with ADHD mainly focused on sleep macrostructure, which pays less attention to the EEG features and phasic phenomena occurring during sleep.

The goal of the present study is to examine the basic neurobiological abnormalities in children with ADHD by "looking beyond the polysomnogram" (Brown, 2006) and studying sleep spindle activity in children with ADHD. Sleep spindles have been suggested to inhibit arousing sensory input and to preserve sleep (Steriade & Timofeev, 2003; Yamadori, 1971), and are generated by the thalamocortical network.

1.4 Sleep Spindles

1.4.1 Definition

N-REM sleep is defined by three basic rhythms: slow oscillations (SO) (frequency of less than 1 Hz), delta (1-4 Hz) and spindles (12-15 Hz). These rhythms are all associated with prolonged hyperpolarizations of thalamocortical (TC) and cortical neurons, which inhibit the transmission of afferent signals. Therefore, these oscillations influence the disconnection of the activated brain to external stimuli, so that sleep will be induced (Steriade, 2006).

Sleep spindles are EEG rhythms oscillating between the frequency of 12 and 15 Hz, grouped in sequences that last for 0.5 to 3 seconds in duration and occur every 3 to 10 seconds (Steriade, McCormick, & Sejnowski, 1993). They are considered as

one of the major hallmarks of transition between wakefulness and sleep. Sleep spindles are highly stable and vary little across nights within the same individual (Shirakawa, Sumizono, & Azumi, 1978; Silverstein & Levy, 1976; Zeitlhofer et al., 1997), suggesting that they could be related to individual traits of functional brain anatomy.

1.4.2 Neurophysiological mechanisms

Sleep spindles are generated by the oscillation of the thalamocortical network (Steriade, 2003). The main elements relevant in the genesis of sleep spindles are the GABAergic thalamic reticular (RE) neurons and the glutamatergic thalamocortical (TC) neurons (Amzica & Steriade, 2000). Spindles originate from the rhythmic inhibitory postsynaptic potentials (IPSPs) of TC neurons by GABAergic thalamic RE neurons (Steriade, 2006), following a reduction in cholinergic transmission to the thalamus. Between inhibition phases, the TC neurons show rebound firing, which entrains cortical populations in spindle oscillations (Steriade, 2006). Thus, the TC and RE cells form a feedback loop with the cortex as schematically shown in Annex 2.

1.4.3 Function of Sleep Spindles

As N-REM sleep rhythms, sleep spindles are associated with prolonged TC and cortical neuron hyperpolarizations that inhibit afferent signal transmission to the brain (Steriade, 2006). Therefore, it has been suggested that the function of sleep spindles is to inhibit arousing sensory input and to preserve sleep (Steriade, 2005; Yamadori, 1971). For example, studies conducted with event-related potential (ERP) have shown that normal waking response of the forebrain to external stimuli is

markedly reduced during spindle occurrence (Steriade, et al., 1993). Thus, researchers hypothesize that sleep spindles serve to raise arousal threshold to inhibit information processing and protect the individual from disturbing sounds in the environment, hence reducing the probability of being awakened (Cote, Epps, & Campbell, 2000; Elton et al., 1997; Johnson, Hanson, & Bickford, 1976). The reports of higher spindle density in hypersomnia support such a role (Bové, Culebras, Moore, & Westlake, 1994).

It has been suggested that sleep spindles are a manifestation of offline memory processing (Gais, Molle, Helms, & Born, 2002; Schabus et al., 2006). For example, Walker *et al.* (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002) used a finger-taping task to demonstrate a significant relationship between improved task performance and amount of Stage 2 NREM sleep spindles. In Schabus *et al*.'s study (Schabus, et al., 2006), a strong relationship between slow and fast sleep spindles with cognitive and memory abilities were found, suggesting sleep spindles do reflect cortical-subcortical connectivity, and are linked to cognitive- and memory-related abilities. More recently, the experiments conducted by Morin and colleagues (Morin, et al., 2008) provided evidence that sleep spindles are involved in the offline motor memory consolidation by showing that there was a large increase in number and duration of sleep spindles following sleep dependent motor learning task. Finally, several researchers have proposed that sleep spindles can be used as a physiological marker of intelligence or general mental ability (Bodizs et al., 2005; Briere, Forest, Lussier, & Godbout, 2000; Fogel, Nader, Cote, & Smith, 2007). Specifically, studies have shown that the number of spindles are positively correlated with performance IQ (PIQ), but not verbal IQ (VIQ). Moreover, there is a relationship between spindles

and PIQ in individuals with higher IQ scores, hypothesising that those high-IQ individuals have more spindles that can support more complex cortical networks underlying perceptual/analytical abilities (Fogel, et al., 2007).

1.4.4 Sleep Spindle Subtypes

There are two types of spindles that differ in their frequency and related brain activations: the activity associated with slow spindles (<13 HZ) are more prominent to the common activation pattern, which involve the thalamus, the anterior cingulated cortex, the left anterior insula, and, bilaterally, the superior temporal gyrus, with the additional recruitment of the right superior frontal gyrus. On the other hand, fast spindles (> 13 Hz) are associated with a number of significant activations beyond the common pattern in the supplementary motor area, sensori-motor, and mid-cingulate cortex. In addition, fast spindles elicit significantly larger responses than slow spindles in the left hippocampus, the orbito and mesial prefrontal cortex, sensori-motor cortex, and anterior insula (Jankel & Niedermeyer, 1985; Schabus et al., 2007). The occurrence of the two types of spindle also differs over one night's sleep. Slow spindles appear predominantly during the early part of sleep, whereas fast spindles generally appear later, towards end of the sleep (Masako, Tatsuya, Hiroshi, & Tadao, 2009).

Given the different spatial and temporal distributions of the two spindle subtypes, it is possible that they also play different roles in learning/cognition (Bodizs, et al., 2005; Schabus, et al., 2006). One study (Tamaki, Matsuoka, Nittono, & Hori, 2008) demonstrated that fast spindles are associated with the learning of a new motor skill, whereas slow spindles appear to display a weak relationship with procedural

memory development. Therefore, studying these two subtypes of sleep spindles will help us understand more about the neurophysiology of children with ADHD.

1.4.5 Spindle activities in children with ADHD

Compared to adults, sleep spindle activity in children of 6 years or older varies with the depth of sleep, being slower as sleep deepens. In 6 to 7 year olds, spindles are of higher voltages, occur early in the night, and have a frequency of 13-15 Hz with parietal-occipital predominance. The frequency may slow to 9-10 Hz later in the night, and mainly in the frontal area. In older children and adolescents, spindles are of lower voltages, 12-Hz spindles occur in deeper sleep and are more pronounced in the frontal area (Fois, 1961; Shibagaki, Kiyono, & Watanabe, 1982). The development of the two types of spindles also show different courses of maturation: fast spindles increase linearly with age, whereas slow spindles rapidly increases during early adolescence (Nagata, Shinomiya, Takahashi, & Masumura, 1996; Shinomiya, Nagata, Takahashi, & Masumura, 1999).

Sleep spindle activity has rarely been examined in children with ADHD. Three studies conducted 20 years ago yielded conflicting results regarding the incidence of sleep spindles in children with ADHD. Kiesow and Surwillo (1987) found no statistically significant differences in the number of sleep spindles between hyperactive and control children. Khan and Rechtschaffen (1978) showed that there were significantly fewer spindles in the EEGs of unmedicated hyperactive children, but that they increased when subjects were treated with methylphenidate. Poitras, Bylsma, Someon, and Pivik (1981) (Poitras, Bylsma, Simeon, & Pivik, 1981) also

reported differences, but in their findings, there were significantly more sleep spindles in the EEGs of unmedicated hyperactive males than normal controls.

It should also be noted that the methodological differences between the three previous studies make it difficult to compare their results directly. EEG patterns from Khan (1978) and Poitras's (1981) study were recorded during a whole night of sleep, while in Kiesow and Surwillow's study (1987), the sleep was induced by Chloral Hydrate during the daytime and only sleep recordings from routine clinical EEGs were analyzed so that the amount of time spent in stage 2 sleep was limited, resulting in fewer sleep spindles detected in their study. All three studies did not mention the diagnostic criteria used for ADHD or the exclusion criteria, and involved only hyperactive boys. Additional methodological shortcomings include small sample sizes, making the ability to generalize from these findings to the larger population of ADHD questionable.

In order to deal with these methodological limitations and to avoid the potential confounding effects of psychiatric or medical comorbidities on the sleep architecture of children with ADHD, children with ADHD and no psychiatric or medical comorbid conditions participated in the current study. In addition, children with primary sleep disorders were excluded from the study. This is important because primary sleep disorders, such as restless legs syndrome (RLS), and sleep disordered breathing (SDB) are common in children with ADHD (Golan, et al., 2004; Sadeh, Pergamin, & Bar-Haim, 2006). These conditions interfere with sleep quality and quantity and lead to symptoms of ADHD in children, such as impaired daytime functioning, causing deficits in attention, memory, executive functioning,

externalizing behaviors (e.g., impulsivity, hyperactivity, aggression), and mood disturbance. However, there is little information regarding sleep in children with ADHD without RLS and SDB. Few studies have attempted to exclude subjects with those primary sleep disorders. Therefore, children with primary sleep disorders were excluded from the current study, as were children with ADHD who suffered from other conditions that affect sleep.

Additional factors shown to moderate the observed associations between sleep characteristics and ADHD include the adaptation to the laboratory environment laboratory environment and the use of stimulant medication (Cortese, et al., 2009). In order to control for the confounding effects of these factors, portable polysomnographic sleep recorders were used to document sleep architectures of children with ADHD and normal controls in each child's natural home environment. The portable PSG devices help to 1) increases the environmental validity of the study; 2) limit the problems associated with laboratory recordings, such as stress or adjustment difficulties, and 3) minimizes the demands on participants, such as traveling. In addition, with the permission of the children's physician and parents, children were asked to be off medication for the duration of the study.

1.5 Hypotheses

The goal of the present study was to compare sleep architecture and sleep spindles activity in children with ADHD and in controls, and to test the following hypotheses:

Hypothesis 1. We expect that compared to control children, children with ADHD will show a lower density (number of spindles per minute of NREM sleep) for slow and fast spindles.

Hypothesis 2. We also predict that children with ADHD will have shorter (sec) fast and slow spindles and lower amplitude (uV) than controls during the NREM sleep.

Hypothesis 3. Finally, we expect that these effects will be more pronounced in the frontal derivations than in the more posterior derivations of the brain.

2. METHODS

2.1 Subjects

Eighteen children (13 males, 5 females) with ADHD (age range = 7-11; mean = 8.94; SD = 1.43) and 26 normal (15 males, 11 females) controls (age range = 7-11; mean = 8.73; SD = 1.28) participated in an on-going study regarding the interplay between the regulation of sleep, neurobehavioral systems and genetic mechanisms in the Attention, Behaviour and Sleep Lab (ABS Lab) at Douglas Mental Health University Institute. The diagnosis of ADHD by a psychologist was based on the criteria of the Diagnostic and Statistical Manual, 4th edition (DSM-IV) (R. Chervin, Hedger, & Dillon, 2000). The Diagnostic Interview Schedule for Children (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) was administered to parents. In addition, in order to achieve consensus between different informants, information regarding ADHD symptoms of each participant was collected from teachers and parents, using the Conner's Behavior Checklist (CBCL) and ADHD Conner's Global Index (CGI) Scale.

Subjects were excluded from the study if they had: 1) a history of mental retardation with an IQ less than or equal to 80, as measured by the Wechsler Intelligence Scale for Children-IV (WISC-IV); 2) a history of autism, Tourette's syndrome, pervasive developmental disorder or psychosis; 3) any medical or psychiatric (Depression, Anxiety) condition that interfered with the ability to sleep; and 4) a major medical condition or impairment that would interfere with the ability to complete testing. None of the children had taken any medication for at least 7 days prior to the assessment. The children were recruited from regular elementary schools in a district whose residents predominantly belong to the middle socioeconomic

classes. This research project was approved by the Research Ethics Board of Douglas Mental Health University Institute. A full explanation of the study was given to parents and children. A consent form was signed by the parent or legal guardian and all children assented to participation in the study. Financial compensation was provided for their participation.

2.2 Study Design

The IQ testing and diagnostic interview was conducted prior to performing in-home sleep recording. Children were asked to be off medication, not to consume products that contained caffeine, complete sleep logs and wear an actiwatch during the night sleep for at least 7 days prior to the polysomnography (PSG) study. Sleep logs and actiwatch data were used to confirm that the PSG night is representative of the child's bedtime and sleep routine. On the scheduled PSG night, a sleep technician arrived at the subject's home around 7pm and hooked-up the sleep recording apparatus. The skin was prepped using alcohol, Nuprep™ abrasive cleanser, and Ten-20™ conductive paste, and tape to attach the electrodes in place. The child went to bed at his/her regular bedtime. The data then was downloaded onto a computer next day.

2.2.1 Sleep measures

The child's sleep was assessed by means of polysomnography (PSG). Signals were recorded using a digital ambulatory sleep recorder (Vitaport-3 System; TEMEC Instruments, Kerkrade, Netherlands), in order to assess the sleep architecture of the children. Standard measures were recorded, including EEGs. EEG electrodes were

placed according to the international 10-20 system (placed bilaterally along the antero-posterior axes at locations F3, F4, C3, C4, P3, P4, O1 and O2) using a referential montage with linked ears, bilateral EOGs and bipolar submental EMGs. Two respiratory belts (one thoracic and one abdominal) and EMG leg electrodes were also used to screen for breathing and leg movement sleep disorders. Signals were digitalized at a sampling rate of 256 Hz using a commercial software product (Harmonie, Stellate System). Sleep stages were scored visually on-screen (LUNA, Stellate System, Montreal) from the C3 derivation (referential derivation, linked ears) according to the standard criteria (Rechtschaffen & Kales, 1968), using 20-second epochs. Sleep structure was characterized by repeated sleep cycles including NREM and REM sleep in a typical sequence. Automatic muscle artifact rejection was performed and then visually checked by an sleep technician (Brunner et al., 1996).

Sleep spindles were automatically detected on F3, F4, C3, C4, P3, P4, O1 and O2 (Mölle, Marshall, Gais, & Born, 2002). To detect slow spindles, data was bandpass filtered from 11–13 Hz using linear phase FIR filter (-3 dB at 11.1 and 12.9 Hz). Forward and reverse filtering were performed to obtain zero-phase distortion and to double the filter order. Root mean square (rms) of the filtered signal was calculated using a 0.25 sec time window. Sleep spindles were identified by thresholding the spindle rms signal at the 95th percentile. The same procedure was followed to detect fast spindles, using a band pass filter of 13-15 Hz (-3 dB at 13.1 and 14.9 Hz). Importantly, sleep spindles were then visually checked. Sleep spindle density was calculated by dividing the total number of spindles in NREM sleep by the total number of minutes in NREM sleep. The automatically spindle detection also record the duration (sec), amplitude (uV) and frequency (Hz) of the spindles.

2.2.2 Behavioral measures

1) CBCL (Achenbach, 1991) is a 113-item parental questionnaire assessing behavioural and emotional problems grouped into eight subscales and three global scales, which include externalizing, internalizing symptoms and total symptoms. Parents provided information for 20 competence items covering their child's activities, social relations, and school performance. Parents rate: 0 = not true; 1 = somewhat or sometimes true; 2 = very true or often true. The CBCL yields good metric characteristics, long term stability (Mattison & Spitznagel, 1999) and excellent representative norms. Reliability and validity of the CBCL has been established repeatedly in both children (Albores-Gallo et al., 2007) and adolescences (Dutra, Campbell, & Westen, 2004).

2) Conners' Global Index-Teacher (CGI-T) (Conners, Sitarenios, Parker, & Epstein, 1998b) and Parent (CGI-P) (Conners, Sitarenios, Parker, & Epstein, 1998a) are widely used instruments designed to evaluate behaviours related to ADHD in both school and home settings. These measures evaluate reported behaviours on 10 items found to be critical to help determine the severity of the problem and whether or not further investigation is necessary. It is ideal for monitoring change over time. Two empirically derived factors are comprised: Restless-impulsive and Emotional Liability, and they were standardized using a large normative database and offer separate norms for boys and girls in 3-year intervals for ages 3 through 17 (Conners, et al., 1998a, 1998b).

2.3 Statistical analysis

One-way analysis of variance (ANOVA) and χ^2 tests were conducted to determine whether the groups differed in demographical characteristics, IQ, or socioeconomic status (SES). To evaluate the impact of gender and group on sleep architectures, two-way ANOVAs with two independent factors (Group and Gender) were performed on polysomnographic sleep variables. To test the hypothesis that there are group differences in sleep spindles, three-way ANOVAs with two independent factors (Group and Gender) and 4 derivations on the left and on the right hemispheres separately as one repeated measure were performed to analyze NREM sleep spindle density, number, amplitude and duration. The Yate's correction was used for ANOVA analyses involving repeated factors. Post-hoc tests were performed when main effects where significant. In all analyses, the level of statistical significance was 0.05. Data was analyzed using the SPSS 15 computerized statistical package.

3. RESULTS

3.1 Demographic characteristics of the study subjects

Table 1 presents means, standard deviations and F values of the demographic and clinical characteristics of the children with ADHD and controls. No significant differences between the controls and the children with ADHD were observed on any of these measures. As expected, significant differences were observed between these groups on the clinical characteristics assessed by using the CBCL. Compared to controls, children in the ADHD group had higher internalizing, externalizing and total problems scores, as well as on the Conners' Parents and Teachers Global Index Scales. Chi-square tests revealed no significant inter-group differences in the children's gender or their parents' marital status.

3.2 Polysomnographic sleep variables

Table 2 shows means and standard deviations of PSG parameters for ADHD and control subjects. There were no significant group or gender differences or interaction between group and gender on any of the measures. Marginal group differences were found for time spent awake after sleep onset ($F = 2.99$, $p = .091$) and sleep efficiency ($F = 3.52$, $p = .068$),

3.3 Average number and density of spindles by derivations and groups

Figures 1 and 2 show average number and density of slow and fast sleep spindles for left and right derivations in children with ADHD and controls. Three-way ANOVAs showed no significant effect of group, gender or interaction with

gender and group. However, significant effects of derivation were found for number and density of slow and fast spindles in left and right derivations ($p < .001$ in all cases). Post-hoc comparisons using the LSD test indicated that the mean density of the frontal derivation ($M = 2.59$, $SD = 0.05$) for the slow spindles was significantly higher ($p < .001$) than the other derivations, whereas the mean density of the occipital derivation ($M = 2.03$, $SD = .08$) was the lowest ($p < .05$) among the other derivations. On the other hand, the mean density for the frontal derivation ($M = .61$, $SD = .05$) for the fast spindles was the lowest ($p <.01$) among the other three derivations, whereas the central derivations ($M = .96$, $SD = .09$) recorded as the highest ($p < .01$) for the fast spindles.

3.4 Analysis for Spindles amplitudes

Figure 3 shows amplitude of slow and fast spindles for the left and the right derivations in ADHD and control subjects. There were no significant effects of group, gender or interaction with gender and group for slow and fast spindle amplitude. Significant effects of derivation were found for amplitude of slow and fast spindles detected in the left and right derivations ($p < .001$, all cases). Post-hoc comparisons using the LSD test indicated that the mean amplitude of the frontal derivation ($M = 12.01$, $SD = .61$) of the slow spindles was significantly higher ($p < .001$) than the other derivations, whereas the mean amplitude of the occipital derivation ($M = 6.34$, $SD = .38$) was the lowest ($p < .001$) among the others. For the fast spindles, the mean amplitudes of the frontal ($M = 5.06$, $SD = .22$) and central ($M = 5.31$, $SD = .23$) derivations are significantly higher ($p < .01$, all cases) than the mean amplitudes of

parietal (M = 4.48, SD = .24) and occipital (M = 3.31, SD = .10) derivations, and the mean amplitude of the occipital derivation was the lowest ($p < .001$).

3.5 Analysis for Spindles Duration

Figure 4 shows the duration of slow and fast spindles for the left and the right derivations in ADHD and control subjects. There were no significant effects of group, gender or interaction with gender and group for slow and fast spindle duration. Significant effects of derivation were found for duration of slow and fast spindles detected in the left and right derivations ($p < .001$, all cases). Post-hoc comparisons using the LSD test indicated that for slow spindles, the mean duration of the parietal derivation was longest ($p < .01$) for both left (M =.88, SD = .01) and right side (M = .88, SD = .02) of brain, whereas for the fast spindles, the mean duration of occipital derivation (M = .75, SD = .01) was the shortest ($p < .01$).

4. DISCUSSION

The goal of the present study was to compare sleep characteristics and examine the differences of NREM sleep spindles between children with ADHD and normal controls. Overnight EEG recordings and polysomnographic analyses were performed in the two groups. An automatic detection algorithm was also used to measure several features (density, amplitude, duration, length) of fast and slow spindles. The results obtained suggested similar sleep architectures between the two groups, and no significant group differences nor any interaction effect between groups in any derivations. The following sections will discuss the results in greater details, and lastly, we will review the limitations and future directions of the present study.

4.1 Polysomnography results in children with ADHD

The result reveals that no significant effect of gender, group, or interaction between gender and group for all sleep variables. Marginal differences were found for awake after sleep onset and sleep efficiency. This is consistent with previous studies showing that children with ADHD have poor sleep and longer sleep latencies (Cortese, et al., 2009) compared to controls. While both groups did not differ on time spent in different stages of sleep, children with ADHD were awake about 15 minutes longer after sleep onset compared with controls. Consistent with previous studies (O'Brien, Holbrook, et al., 2003; O'Brien, Ivanenko, et al., 2003), REM sleep latency of children with ADHD was 25 minutes longer compared to controls, although this difference did not reach significance. REM sleep has been associated with learning and performance, particularly with measures of executive functions, attention,

memory and language, a delayed in reach REM sleep could result a decrease in REM percentage, which has been correlated with deficits in these functions (Siegel, 2001). Therefore, by using portable polysomnographic sleep recorders in each child's natural home environment, our sample of children with ADHD without other significant sleep disorders (i.e. apneas, RLS) showed no disturbance of sleep when compared with controls. However, we are unable to determine if those children were underaroused. Future studies should evaluate children's sleepiness level by using means of MSLT or waking EEG.

4.2 Spindle in children with ADHD

4.2.1 Number and density of sleep spindles

Number and density of sleep spindles were measured to study sleep/arousal mechanisms in children with ADHD, and the results of the present study showed that there were no differences in children with ADHD compared with those without the attention and hyperactive problems for those two measures. Our results suggest that sleep spindle activity, as expressed by its number and density presently identified in the ongoing EEG, is not one of the underlying mechanisms for the hypoarousal in children with ADHD. The significant effects of derivation confirmed the presence of 2 independent sleep spindle components and their scalp distributions (Gibbs & Gibbs, 1964; Shinomiya, et al., 1999). This indicates that slow spindles (11-13Hz) were more prominent whereas fast spindles (13-15Hz) were less prominent in the frontal region in both left and right hemispheres of the brain. The fast spindles activity is maximal over the central scalp region.

4.2.2 Amplitude and duration of sleep spindles

To our knowledge, this is the first study assessing amplitude and duration of sleep spindles in children with ADHD. In the present study, there were no group or gender differences in the amplitudes and duration of slow and fast spindle. Similar to the amplitudes of sleep spindles, the mean duration of sleep spindles did not show any difference between the two groups. However, a significant effect of derivation was found for amplitude in all slow and fast spindles. In both slow and fast spindles, amplitudes were highest in the frontal/central area and lowest in the occipital. It is consistent with the finding that sleep spindles were most prominent and of highest amplitude just anterior to the midline central regions (Brazier, 1949; Jasper & Andrews, 1938; Zeitlhofer, et al., 1997).

4.3 Limitations and Future Directions

There are some limitations to the present study that deserve mentioning. First, our sample size included only 18 subjects in the ADHD group and 26 in the control group. Although it was a fairly adequate sample size for a sleep study of this nature, we were unable to directly study the heterogeneity in the ADHD subtypes. With nearly 72% of ADHD-combined subtype (13 ADHD-combined and 5 ADHD-inattentive in our ADHD group), we did not have enough statistical power to further study the data with respect to the ADHD subtypes. As several studies suggest that children with ADHD may represent a heterogeneous group with different underlying electrophysiological abnormalities (Barry, Clarke, & Johnstone, 2003; Clarke, Barry, McCarthy, & Selikowitz, 1998; Hermens, Kohn, Clarke, Gordon, & Williams, 2005).

In addition, while the ADHD-combined subtype showed increased beta activity compared to ADHD-inattentive subtype, there is a topographic difference in EEG between genders in children with ADHD: ADHD-combined males showed increases frontally, whereas ADHD-combined females showed increased activity at centro-posterior sites (Hermens, et al., 2005). This difference is in line with the general decrease in posterior beta activity for ADHD females, regardless of subtype (Hermens, et al., 2005). Analysis of sleep spindles in gender and different subtypes of ADHD will help us to better understand the underlying biological difference and the deficits in arousal/attention systems underlying the behavioural expression of ADHD, this is perhaps a point for future studies.

A second limitation is that sleep spindles were scored by an automatic detection algorithm that is designed for detection in adults, and sleep spindles were identified by thresholding the spindle rms signal at the 95th percentile. According to "the visual scoring of sleep and arousal in infants and children" (Grigg-Damberger et al., 2007), for children younger than 13 years of age, sleep spindles occur independently at two different frequencies and two different scalp locations: 11.0-12.75 Hz over the frontal and 13.0-14.75 Hz over the centroparietal areas. In the current study, sleep spindles were detected at 11-13 Hz for the slow spindles and 13-15 Hz for the fast spindles. It is possible that sleep spindles in children may slow to 9-10 Hz later in the night (Masamitsu, Sigehiro, & Kazuyoshi, 1982). Consequently, the current detection algorithm increased the chance of computing false negative, therefore, the criteria of automatic spindles detection algorithm could be set differently, (i.e., slower frequency) in future studies.

To further explore sleep spindle activities in children with ADHD, two future directions could be put into the research agenda: the function of sleep spindles in memory and learning, and its role in sleep deprivation.

4.3.1 Sleep spindles in memory and learning

ADHD is frequently accompanied by comorbidities such as learning disabilities. As sleep spindles have raised the researcher's interests in their roles in the learning and memory consolidation process, it is essential to study if sleep spindles play a role in those processes in children with ADHD. For example, Walker and his team (Walker, et al., 2002) used a finger-taping task, and demonstrated a significant relationship between improved task performance and amount of Stage 2 NREM sleep spindles. A recent study (Tamaki, et al., 2008) observed a significant relationship between visuomotor performance and fast spindles, suggesting the thalamocortical network underlying fast-spindle generation may contribute to plasticity during sleep. However, those studies have only been conducted in adults. The replication of such studies in children is necessary to further investigate the different neural development in children with ADHD.

4.3.2 Sleep spindles in sleep deprivation

Based on common sense, inadequate sleep makes children more moody, more impulsive and less able to concentrate; these are the same symptoms as in the ADHD diagnosis. Therefore, observing the activity of sleep spindles in studies targeting children with ADHD during sleep restriction and during sleep deprivation, or on a recovery night after they have been experimentally sleep deprived might provide

additional information on the sleep-protection role of sleep spindles and further guide us on the recovery processes in this population.

5. CONCLUSION

The objective of the present study was to examine the difference in sleep spindle activity between children with ADHD and controls. The results showed that sleep spindle activity did not differ between children with ADHD and normal controls in terms of number, amplitude, length and density. Altogether, the results suggest that sleep/arousal mechanisms, as expressed by the number and density of sleep spindles presently identified in the ongoing EEG, are not different in children with ADHD compared with those without the attention and hyperactive problems.

Table 1

Demographic and clinical characteristics of children with ADHD and Controls

	ADHD (N=18)	Controls (N=26)	Total (N=44)	
Age (M/SD)	8.94 (1.43)	8.73 (1.28)	8.82 (1.33)	$F = .27$, $df = 1$, n.s
Gender Male(Female)	13 (5)	15 (11)	28 (16)	$\chi^2 = .97$, $df = 1$, n.s
SES	49.64 (9.61)	46.36 (12.07)	47.87 (10.99)	$F = .86$, $df = 1$, n.s
Parent Marital status				
Married	14	20	34	
Separated	1	0	1	
Divorced	0	4	4	$\chi^2 = 4.97$, $df = 3$, n.s
Single	3	2	5	
		102.96		$F = .72$, $df = 1$, n.s
WISC full scale	98.13 (20.2)	(16.52)	101.12(17.72)	
CBCL T-Score				
Total problem	62.61 (8.23)	50.62 (9.91)	55.52 (10.93)	$F = 17.83$***, $df = 1$
Internalizing problem	62.39 (9.20)	51.96 (10.93)	56.23 (11.39)	$F = 10.98$**, $df = 1$
Externalizing problem	57.83 (9.1)	50.42 (9.14)	53.45 (9.74)	$F = 7.01$*, $df = 1$
CGI-Teacher T Score	61.25 (16.94)	50.16 (7.4)	55.23 (13.67)	$F = 23.15$***, $df = 1$
CGI-Parents T Score	65 (12.07)	50.32 (7.95)	56.47 (12.20)	$F = 6.67$*, $df = 1$

N: Number;

M: Mean;

SD: Standard Deviation;

SES: Socioeconomic Status;

PPS: Petersen's Pubertal Score;

CBCL: Child Behavior Checklist;

CGI: Conner's Global Index

***$p < .001$

**$p < .01$

*$p < .05$

Table 2 Means (Standard Deviations) for Sleep Variables

Sleep Variables	***ADHD (N = 18)***	***Controls (N = 26)***	
Sleep latency (min)	30.1 (18.6)	26.8 (18.7)	$F = .12$, $p = .73$
Total sleep time (min)	518.1 (44.2)	530.6 (45.9)	$F = .52$, $p = .47$
Total awakening time (min)	29.5 (24.6)	14.1 (7.4)	$F = 2.99$, $p = .09$
Sleep efficiency (%)	93.9 (4.2)	96.7 (1.3)	$F = 3.52$, $p = .07$
Number of shifts/h sleep	39.2 (7.1)	39.3 (7.7)	$F = .02$, $p = .89$
Stage 1			
Total time (min)	22.6 (11.1)	20.2 (10.1)	$F = .94$, $p = .34$
Proportion (%)	4.3 (2.1)	3.9 (2.1)	$F = .89$, $p = .35$
Stage 2			
Total time (min)	223.9 (34.1)	223 (44.7)	$F = .04$, $p = .84$
Proportion (%)	43.2 (5.2)	42 (7.3)	$F = .46$, $p = .5$
Stage 3			
Total time (min)	69.9 (21.2)	76.4 (19.8)	$F = 1.34$, $p = .26$
Proportion (%)	13.5 (3.8)	14.4 (3.7)	$F = .91$ $p = .35$
Stage 4			
Total time (min)	106.5 (19.7)	108.3 (31.7)	$F = .15$, $p = .7$
Proportion (%)	20.7 (4.1)	20.5 (6.2)	$F = .03$, $p = .87$
REM			
Total time (min)	109.2 (25.3)	118.0 (26.8)	$F = .56$, $p = .46$
Proportion (%)	18.3 (4.3)	19.2 (3.3)	$F = .29$, $p = .59$
Latency to REM	123.5 (29.3)	147.2 (33.2)	$F = .77$, $p = .39$

Figure 1

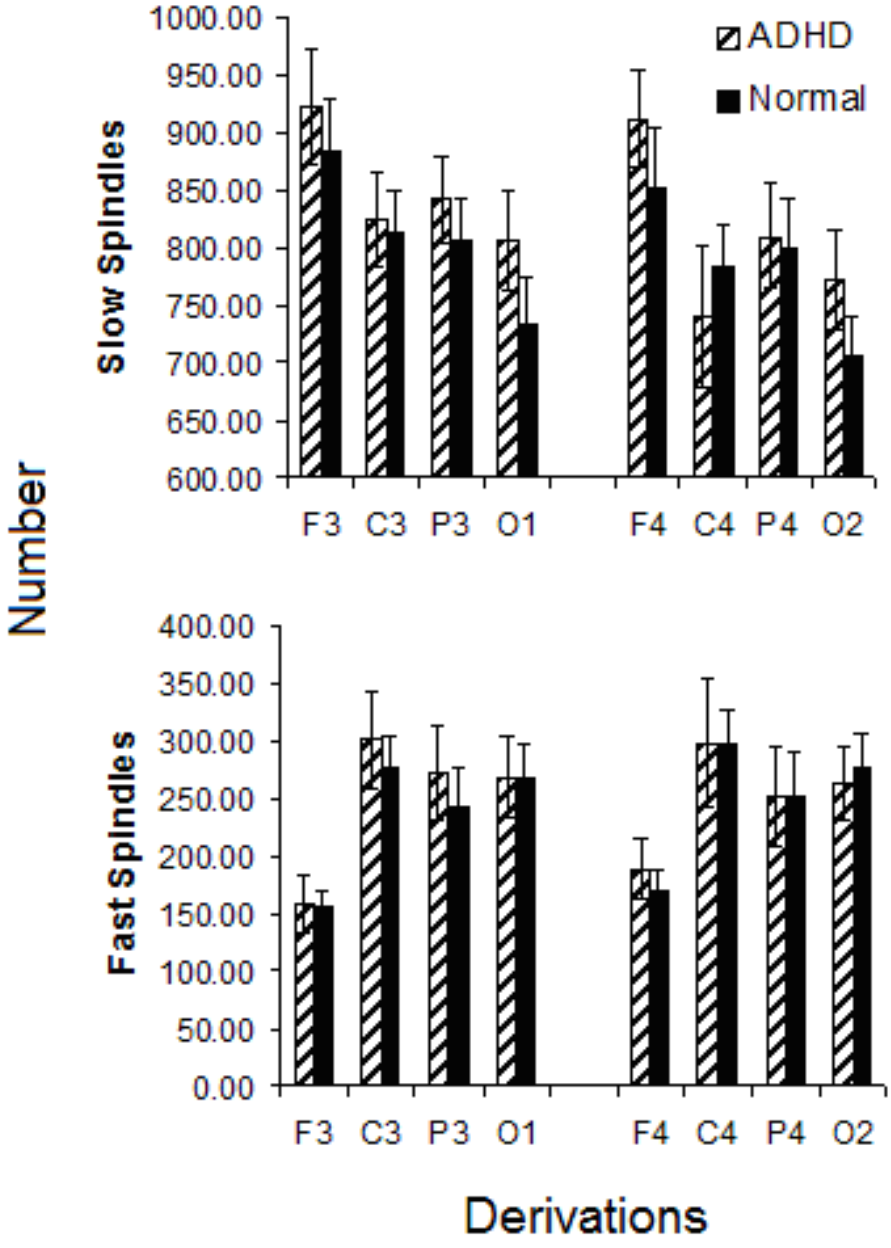

ADHD
Normal
Slow Spindles
1000.00
950.00
900.00
850.00
800.00
750.00
700.00
650.00
600.00
F3 C3 P3 O1 F4 C4 P4 O2
Fast Spindles
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
F3 C3 P3 O1 F4 C4 P4 O2
Number
Derivations

Figure 2

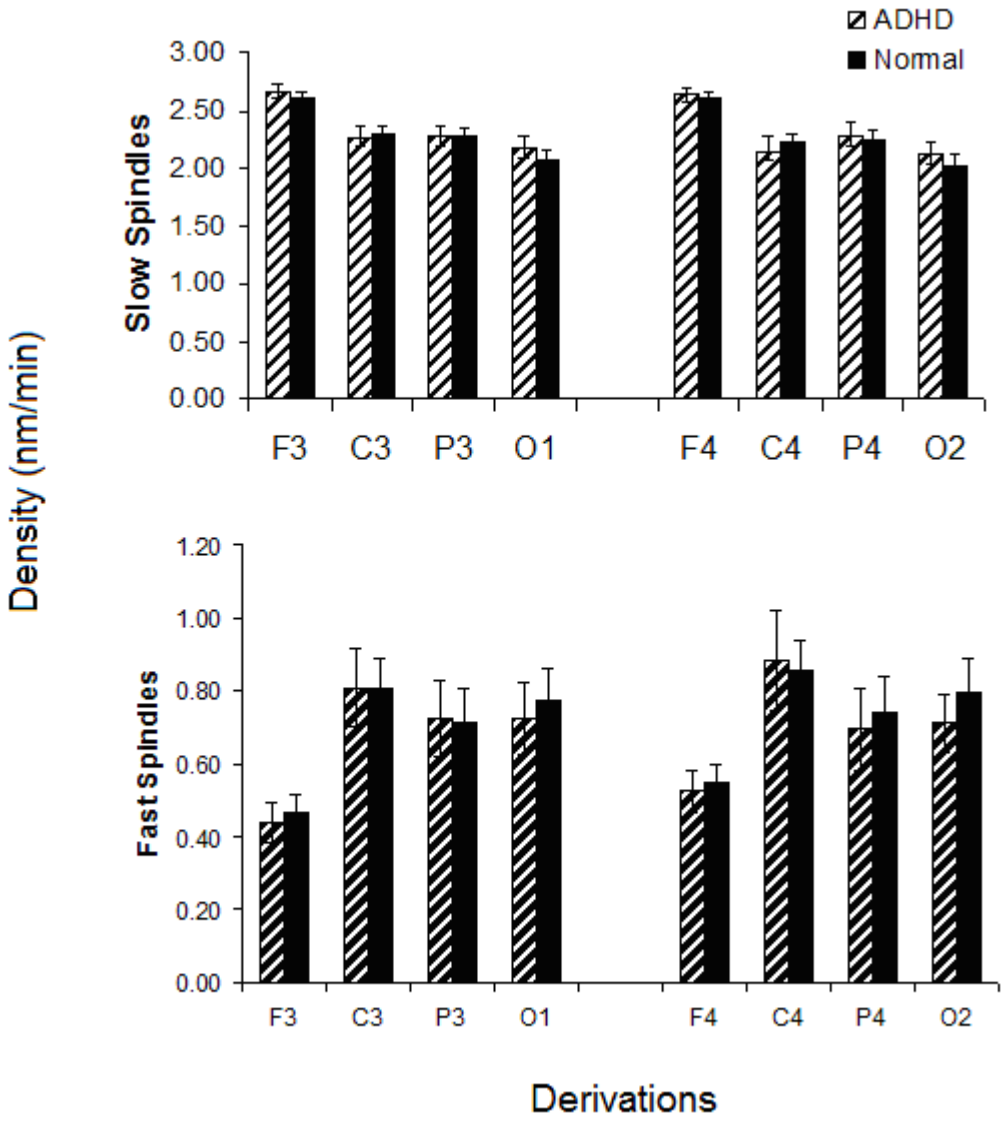

ADHD
Normal
Slow Spindles
3.00
2.50
2.00
1.50
1.00
0.50
0.00
F3
C3
P3
O1
F4
C4
P4
O2
Fast Spindles
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Density (nm/min)
Derivations

Figure 3

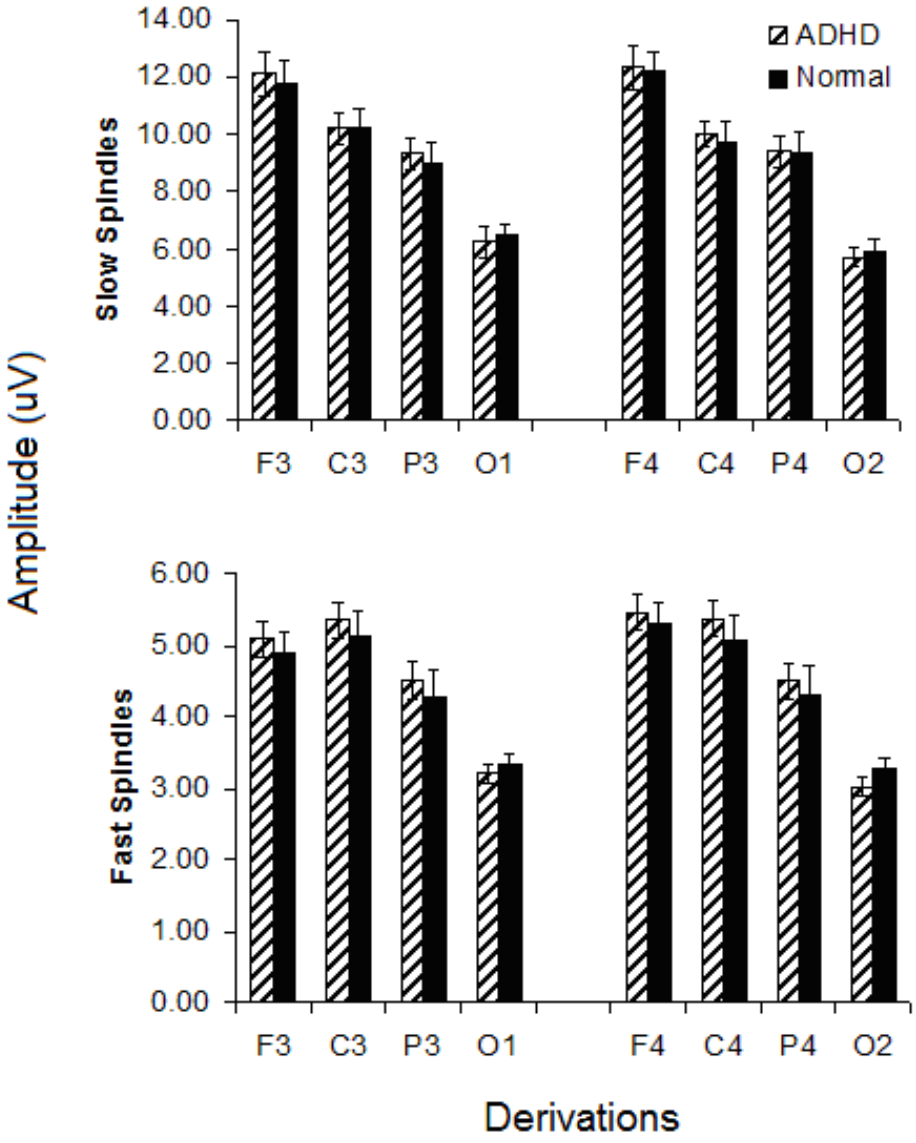
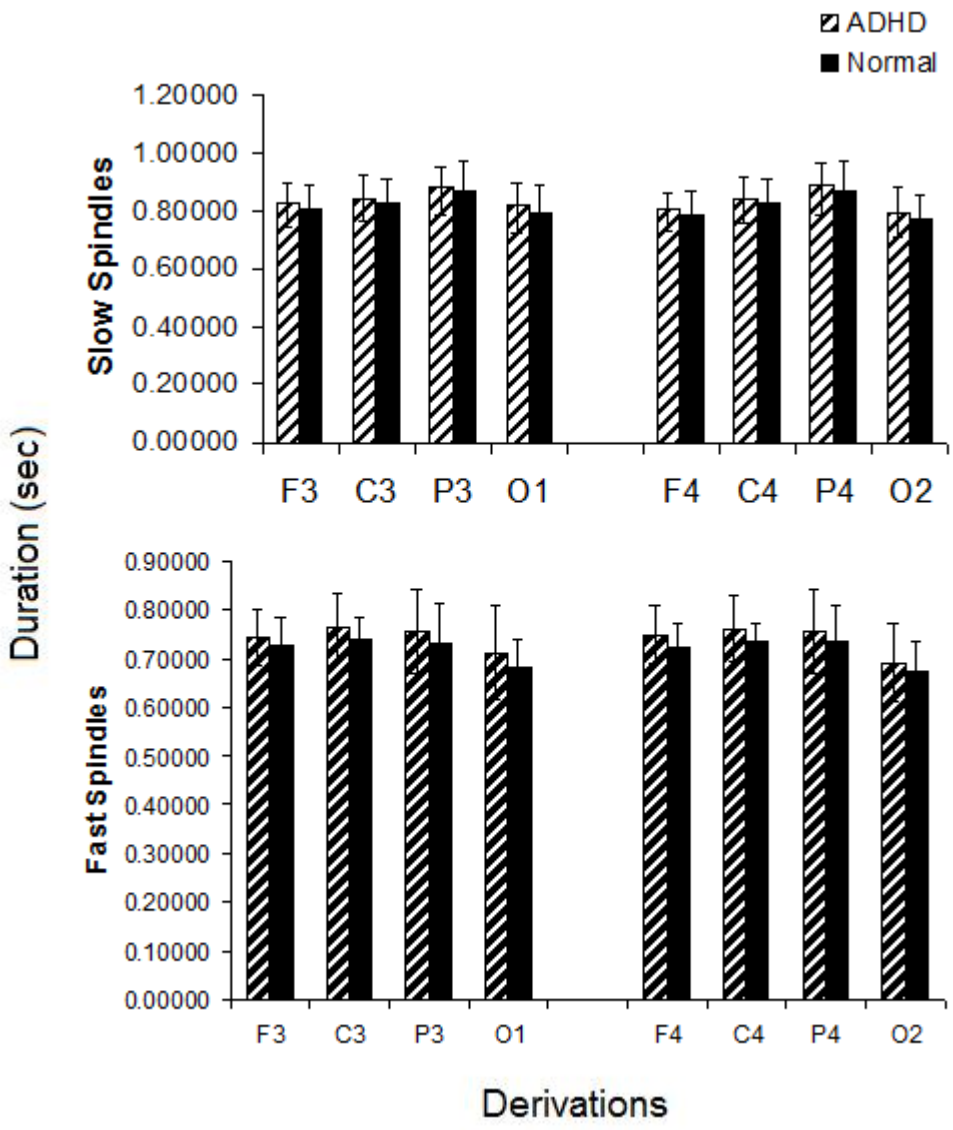

Amplitude (uV)
Slow SpIndles
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
ADHD
Normal
F3
C3
P3
O1
F4
C4
P4
O2
Fast SpIndles
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Derivations

Figure 4


ADHD
Normal
Slow Spindles
1.20000
1.00000
0.80000
0.60000
0.40000
0.20000
0.00000
F3
C3
P3
O1
F4
C4
P4
O2
Fast Spindles
0.90000
0.80000
0.70000
0.60000
0.50000
0.40000
0.30000
0.20000
0.10000
0.00000
Duration (sec)
Derivations

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ANNEXE 1

TABLE 1. Diagnostic Criteria for ADHD

A. Either 1 or 2
  1) Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention
  a) Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
  b) Often has difficulty sustaining attention in tasks or play activities
  c) Often does not seem to listen when spoken to directly
  d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
  e) Often has difficulty organizing tasks and activities
  f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
  g) Often loses things necessary for tasks or activities (eg, toys, school assignments, pencils, books, or tools)
  h) Is often easily distracted by extraneous stimuli
  i) Is often forgetful in daily activities

  2) Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity
  a) Often fidgets with hands or feet or squirms in seat
  b) Often leaves seat in classroom or in other situations in which remaining seated is expected
  c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
  d) Often has difficulty playing or engaging in leisure activities quietly
  e) Is often "on the go" or often acts as if "driven by a motor"
  f) Often talks excessively

Impulsivity
  g) Often blurts out answers before questions have been completed
  h) Often has difficulty awaiting turn
  i) Often interrupts or intrudes on others (eg, butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before 7 years of age.
C. Some impairment from the symptoms is present in 2 or more settings (eg, at school [or work] or at home).
D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.
E. The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (eg, mood disorder, anxiety disorder, dissociative disorder, or personality disorder).

Code based on type:

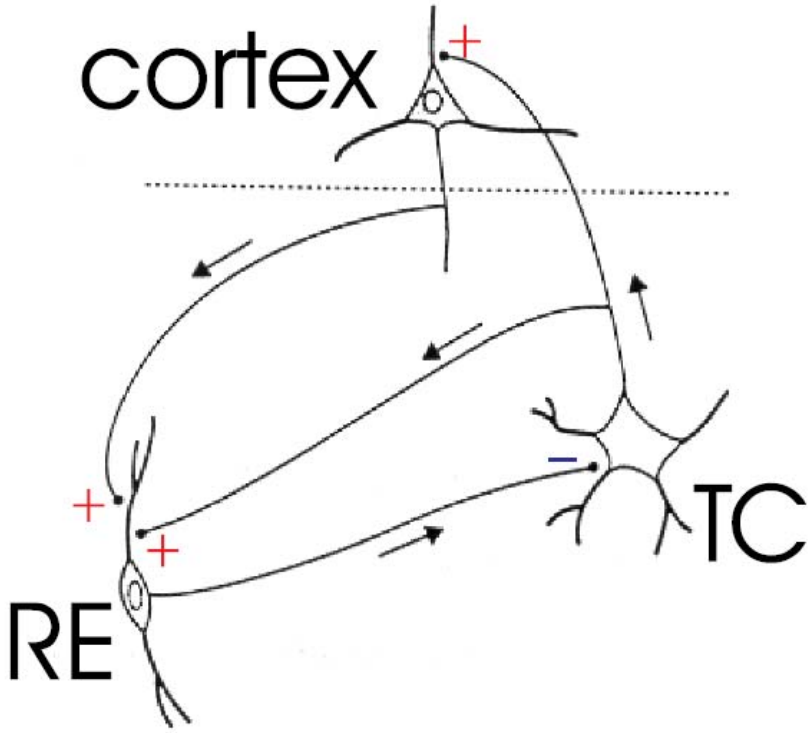
314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if criterion A1 is met but criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive, Impulsive Type: if criterion A2 is met but criterion A1 is not met for the past 6 months

314.9 Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified

ANNEXE 2



The scheme of thalamic network in which spindles are generated. Sign "+" indicates excitatory synaptic connection, "-" indicates inhibitory synaptic connection. Adapted from (Steriade, 1993)