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The sleep phenotypes of attention deficit hyperactivity disorder: The role of arousal during sleep and implications for treatment

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ABSTRACT

About 25–50% of children and adolescents with attention-deficit hyperactivity disorder (ADHD) experience sleep problems. An appropriate assessment and treatment of such problems might improve the quality of life in such patients and reduce both the severity of ADHD and the impairment it causes. According to data in the literature and to the overall complexity of the interaction between ADHD and sleep, five sleep phenotypes may be identified in ADHD: (i) a sleep phenotype characterized mainly by a hypo-arousal state, resembling narcolepsy, which may be considered a "primary" form of ADHD (i.e. without the interference of other sleep disorders); (ii) a phenotype associated with delayed sleep onset latency and with a higher risk of bipolar disorder; (iii) a phenotype associated with sleep disordered breathing (SDB); (iv) another phenotype related to restless legs syndrome (RLS) and/or periodic limb movements; (v) lastly, a phenotype related to epilepsy/or EEG interictal discharges.

Each sleep phenotype is characterized by peculiar sleep alterations expressed by either an increased or decreased level of arousal during sleep that have important treatment implications. Treatment with stimulants is recommended above all in the primary form of ADHD, whereas treatment of the main sleep disorders or of co-morbidities (i.e. bipolar disorders and epilepsy) is preferred in the other sleep phenotypes. All the sleep phenotypes, except the primary form of ADHD and those related to focal benign epilepsy or focal EEG discharges, are associated with an increased level of arousal during sleep. Recent studies have demonstrated that both an increase and a decrease in arousal are ascribable to executive dysfunctions controlled by prefrontal cortical regions (the main cortical areas implicated in the pathogenesis of ADHD), and that the arousal system, which may be hyperactivated or hypoactivated depending on the form of ADHD/sleep phenotype.

Introduction

About 25–50% of children and adolescents with attention-deficit hyperactivity disorder (ADHD) experience sleep problems [1]. An appropriate assessment and treatment of such problems might improve the quality of life in such patients and reduce both the severity of ADHD and the impairment it causes. Indeed, a better characterization and understanding of the specific sleep alterations underlying these complaints is needed [2]. Subjective sleep problems, as reported above all by caregivers, are bedtime resistance, sleep onset difficulties, increased number of night awakenings, difficulties with morning awakenings, sleep disordered breathing and daytime sleepiness. Objective data based on actigraphic recordings demonstrate an increase in sleep onset latency, associated with a decreased amount of time spent asleep, while those obtained by polysomnographic studies show an increased number of stage shifts, an increased apnea-hypopnea index during sleep and a decrease in the time taken to fall asleep as measured by the Multiple Sleep Latency Test. Moreover, although the suggestion that the number of general sleep movements and periodic limb movements is higher in children with ADHD than in controls remains controversial, a meta-analysis study designed to investigate sleep and ADHD confirms this hypothesis [3].

Moreover, it has been reported that children with ADHD showed daytime hypersomnolence and the excessive diurnal motor activity might be a strategy to counteract sleepiness. However, the exact nature of excessive daytime sleepiness has yet to be determined. Indeed, excessive daytime sleepiness might the consequence of a primary disorder due to a state of hypo-arousal during sleep or of other sleep disorders, such as those described above. Numerous neuroimaging and electroencephalographic (EEG) studies in children with ADHD have demonstrated a low degree of arousability in frontal, central and midline regions [3,4].

Another important factor implicated in the pathogenesis of sleep instability is the increased rate of EEG-documented interictal discharges during sleep in children with ADHD compared with normal controls [5]. Moreover, population studies have shown a

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high prevalence of ADHD in childhood epilepsy, which ranges between 12% and 17% [6]. Several mechanisms may account for the high prevalence of EEG discharges and epilepsy in children with ADHD, such as a common genetic propensity, noradrenergic system dysregulation, subclinical epileptiform discharges (or seizures), as well as psychosocial factors that may affect cognition and sleep, even in the absence of clinical or subclinical seizures [7].

Lastly, the relationship between sleep disordered breathing (SDB), sleep instability and ADHD has been widely reported. Indeed, children with SDB are known to be affected by diurnal neurobehavioral problems such as ADHD, learning problems, behavioral disorders and hypersomnolence [8]. Findings from previous studies suggest that intermittent hypoxia during sleep, respiratory events and sleep fragmentation are the main causative factors of the diurnal neurobehavioral consequences of obstructive sleep apnea syndrome (OSAS) [9].

According to data in the literature and to the overall complexity of the interaction between ADHD and sleep, five sleep phenotypes may be identified in ADHD: (i) a sleep phenotype characterized mainly by a hypo-arousal state, resembling narcolepsy, which may be considered a "primary" form of ADHD (i.e. without the interference of other sleep disorders); (ii) a phenotype associated with delayed sleep onset latency and with a higher risk of bipolar disorder; (iii) a phenotype associated with sleep disordered breathing (SDB); (iv) another phenotype related to restless legs syndrome (RLS) and/or periodic limb movements (PLMDs); (v) lastly, a phenotype related to epilepsy/or EEG interictal discharges.

Each sleep phenotype will be assessed in detail and the implications of sleep alterations (in terms of increased or decreased level of arousal during sleep) for the treatment and management of clinical diurnal ADHD will be discussed.

"Primary ADHD": the sleep model of the hypo-arousal state resembling narcolepsy

A dysfunction in arousal mechanisms resembling that observed in narcolepsy has been hypothesized in the etiology of ADHD, with motor hyperactivity being considered a reaction to the hypo-arousal condition that is required to counteract somnolence [10]. Children with ADHD have been reported to be significantly sleepier during the day than control children, with shorter sleep latencies and diurnal hypersomnolence, particularly in children with sleep limb movement disorders [11].

Cyclic alternating pattern (CAP) analysis during NREM, which is the EEG marker of unstable sleep, has been described as one of the most systematic and expressive constructs devised to describe arousals, their composition and their timing during sleep [12]. NREM sleep is characterized by an oscillating pattern that exhibits different levels of arousal. This physiological oscillating pattern, coded as CAP, is considered important for sleep building and maintenance [13]. CAP is composed of an EEG transient pattern (phase A of the cycle) separated by intervals of background activity (phase B of the cycle). The three main EEG patterns differ according to the prevalence of EEG synchrony (subtype A1), prevalence of EEG desynchrony (subtype A3), or a combination of both (subtype A2) [14]. In disorders characterized by hypo-arousability (narcolepsy, ADHD and Prader Willy syndrome), there is a global decrease in NREM instability, represented by a reduction in the CAP rate and A indexes [15]. In particular, a cohort of children with ADHD without sleep disorders displayed a lower CAP rate and a lower number of CAP sequences than normal controls, as well as a decreased A1 index, mainly during light sleep (sleep stages 1 and 2) [15]. Similar CAP parameters were found in both adults and children with narcolepsy [16,17]. These findings point to the existence of a hypo-arousal state in children with ADHD. The excessive stability of NREM sleep observed in ADHD children, who were selected on the basis of the absence of other sleep disorders and were consequently considered to be affected by "primary ADHD", may have strong implications on cognitive functions, on executive dysfunctions and on learning disability co-morbidity. However, these sleep microstructure alterations detected by CAP analysis were not recently confirmed in another cohort of children with ADHD without sleep disorders [18].

The core symptoms of ADHD can be effectively treated by means of various medications, including methylphenidate (MPH), amphetamine and pemoline, as well as the new extended-release $\alpha 2$ adrenergic agonists, which have also been used in narcolepsy to reduce and to contrast diurnal sleepiness. Although no studies have been conducted on the effects of stimulants on NREM sleep stability/instability, as analyzed by CAP, we believe that treatment with stimulants are indicated in this sleep phenotype of ADHD, which resembles the narcolepsy sleep model, as well as in those children with ADHD in whom sleep problems are not reported or have objectively been ruled out, or who only display diurnal hypersomnolence. Most of these drugs are known to affect sleep because of their pharmacological action on dopaminergic and/or noradrenergic release in the central nervous system. Previous studies have found an increased incidence of insomnia and sleep disturbances in ADHD children treated with central nervous system stimulants [19]. By contrast, recent prospective, double-blind, placebo-controlled trials showed that MPH does not cause significant sleep problems in children or adolescents with ADHD studied by objective polysomnographic or actigraphic recordings [19], though do not data exist on the effects of MPH(+) on sleep instability, as measured by arousal and CAP analysis.

Sleep onset delay insomnia in ADHD and co-morbidity with bipolar disorder: a model of increased arousability during sleep in children with ADHD

The most common sleep problem in children with ADHD is insomnia, which consists in delayed sleep onset, sleep or bedtime resistance, prolonged tiredness upon waking and daytime sleepiness [20]. Van der Heijden et al. described two cohorts of children with ADHD who manifested sleep-onset insomnia (an ADHD-SOI phenotype) [21,22]. When compared with ADHD children without sleep onset insomnia, ADHD-SOI children exhibited delayed sleep-wake cycles, delayed dim-light melatonin onsets and significantly lengthened sleep latencies, though no difference emerged in total sleep time [21,22]. The ADHD-SOI phenotype may account for as many as 30% of children diagnosed with ADHD [23].

A marker of the earliest forms of pediatric bipolar disorder (BD) is co-morbidity with disruptive behavior disorders, particularly ADHD [24,25]. A higher rate of BD has been observed in a relatively large sample of Italian children with ADHD (29/173, 16.7%), if compared with normal controls (1/100, 1%). Moreover, when compared with ADHD children without BD, ADHD children with BD displayed a higher rate of combined sub-type ADHD (21/29, 72.4%), a higher ADHD Rating Scale score (total score and hyperactivity subscale), as well as higher rates of major depression, oppositional defiant disorder and conduct disorder [26].

Preliminary evidence from severe mood dysregulation related disorders, such as ADHD and pediatric BD, indicates that morning light therapy has a positive effect on depressive symptoms, circadian rhythms, inattention and irritability [27]. Staton [28] recently suggested that the core endophenotypic characteristic of pediatric bipolar sleep is a phase-delayed circadian sleep-wake cycle, rather than a reduced need for sleep per se, i.e. pediatric bipolar sleep insomnia is similar to that of ADHD-SOI children. Children and adolescents with part-day manic cycles and chronic mixed

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conditions typically manifest delayed sleep onset, though not a decreased need for sleep, while those with days-long manic cycles or chronic mania typically manifest a decreased need for sleep, which is due to the interaction between the sleep-onset phase delay and bedtime and early morning manic psychomotor acceleration. Childhood co-occurrence of SOI and ADHD symptoms should prompt clinical exclusion of bipolar disorder, e.g. variants of pediatric bipolar types IIA, IIB and IIIA [28].

There is no clear evidence that stimulants or selective serotonin reuptake inhibitor accelerate or exacerbate the development of BD in children with ADHD, though physicians should act with caution when using these agents in youths who are at risk of developing BD, such as those with ADHD and mood dysregulation, a history of prior antidepressant-induced mania, a history of psychosis, a family history of BD or a history of SOI. Melatonin improves the sleep-wake rhythm and endogenous melatonin rhythm in delayed sleep phase disorder [28]. Several studies have evaluated the efficacy and safety of melatonin for the treatment of insomnia in pediatric patients with ADHD, with melatonin doses ranging between 3 and 6 mg being administered within a few hours of a scheduled bedtime [29,30]. In conclusion, we suggest that circadian rhythmic disorders in children with ADHD-SOI should be treated with melatonin and/or light therapy so as to avoid the use of stimulants, particularly in those at risk of developing bipolar disorder; the administration of second-generation antipsychotic drugs, such as aripripazole or risperidone, be preferred in the latter group of patients [31,32].

We hypothesize that the sleep fragmentation and reduced total sleep time in ADHD-SOI result in sleep deprivation and diurnal neurobehavioral problems. We may argue that they express an increased level of arousal during the day, at bedtime and at night, as occurs in insomnia during adulthood, though no data are available relative to arousal during sleep in children with ADHD-SOI [33,34].

Ostructive sleep apnea syndrome phenotype: a model of increased arousability during sleep in children with ADHD

Numerous studies designed to investigate the association between ADHD and sleep disordered breathing have shown that children with ADHD may have a relatively mild form of OSAS, with an apnea-hypopnea index (AHI) that is, despite being moderate (between 1 and 5 events per hour of sleep), suggestive of pediatric obstructive sleep apnea [2].

Numerous other studies have investigated the association between diurnal neurobehavioral problems, such as ADHD, learning problems, behavioral disorders and hypersomnolence, and sleep-disordered breathing (SDB) [35]. Findings from these studies suggest that intermittent hypoxia during sleep, respiratory events and sleep fragmentation are the main causes of the diurnal neurocognitive consequences of obstructive sleep apnea syndrome (OSAS) [9,36]. One study conducted on a large cohort of children demonstrated that the degree of hypoxemia correlates with deficits in executive function [9], whereas the degree of sleep fragmentation, as expressed by the number of arousals during sleep in response to respiratory events, appears to account for changes in attention and memory deficits [37–39]. The neurocognitive phenotype of pediatric OSAS may reflect a dysfunction in the prefrontal cortex (PFC), which controls executive functions and contains the brain areas that mature last, and might thus be susceptible to OSA-mediated injury [40]. The same PFC regions generate slow oscillations during NREM sleep, which are the main components of the A1 subtypes of CAP and map over the frontal and prefrontal regions of the scalp [41]. The few data available on CAP in pediatric SDB are somewhat contradictory [42–46]. In one study, children with SDB had a lower CAP rate, particularly during slow-wave sleep, with no clear increase in the number of arousals if compared with normal controls [44]. By contrast, Lopes and Guilleminault [43] found an increased CAP rate in children who snored as well as in sleepwalking children with SBD [42]. Moreover, a positive correlation between the increased CAP rate and behavioral complaints was found in children who habitually snored [43,46]. We have also reported a higher CAP rate during slow-wave sleep and an increased A2 index in children with OSAS compared with normal controls [45], as well as a positive correlation between total ADHD Rating Scale scores and hyperactivity scores with the A2 index, while the hyperactivity rating score correlated negatively with night-time oxygen saturation [46]. These results support the hypothesis that arousal (expressed by the A2 components of the CAP) is a defensive mechanism that may preserve cognitive function by counteracting the intermittent hypoxia due to respiratory events, at the expense of sleep maintenance and NREM sleep instability assessment, and at the expense of diurnal ADHD [46]. Increased arousal enhances sympathetic activity during sleep. The increase in the level of arousal during sleep in children with OSAS is indirectly confirmed by the fact that sympathetic activity increases during sleep, as demonstrated by the analysis of heart rate variability (HRV), and decreases after adenotonsillectomy [47]. We have recently demonstrated that children with OSAS have increased basal sympathetic activity during wakefulness as well as a negative reaction, which varies according to the severity of OSAS, to several physiological stimuli [48].

All these findings suggest that the arousal level in the sleep phenotype of ADHD associated with OSAS is increased during both daytime and sleep. We suggest that OSAS be treated before daytime stimulant administration is started since stimulants increase sympathetic activity, and we do not know whether this sleep phenotype of ADHD has any long-term effects on the cardiovascular system. We also suggest that other kinds of stimulants with cholinergic effects, such as *Ginkgo biloba* extract (EGb 761), should be used if severe neurobehavioral symptoms persist after the treatment and resolution of SDB. This phytotherapic compound has recently been reported to protect against intermittent hypoxia-induced memory deficits and hippocampal DNA damage in rats [49], to improve working memory in normal, healthy middle-aged men [50], and to reduce dyslexia in children [51]. Moreover, a recent double-blinded randomized controlled trial in children demonstrated that *Ginkgo biloba* improves ADHD symptoms, though to a lesser extent than methylphenidate [52].

Restless legs syndrome (RLS) and periodic limb movements during sleep: a model of increased arousability in children with ADHD

Periodic leg movements in sleep (PLMS) are episodes of repetitive and stereotypic leg movements that occur during sleep. Children with periodic limbs movements and/or restless legs syndrome may display daytime symptoms of hyperactivity, impulsivity, inattentiveness and decreased school performance. Physicians should consider PLMS in the differential diagnosis of a child with ADHD symptoms [53].

Although it is not possible to pool data from movement measurements in sleep (general movements and periodic limb movements in sleep) owing to differences in the indexes used to quantify movements in sleep, a descriptive analysis of the data in the literature does indicate that general sleep movements and periodic limb movements may occur significantly more often in children with ADHD than in controls [3]. The possible role of brain iron availability in this ‘‘ADHD secondary form’’ has recently been highlighted [54]. Indeed, since brain iron is expected to impact on the neuronal functions and myelination of white matter, which

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underpin ADHD symptoms, it has been suggested that, besides an assessment of peripheral iron markers, an estimation of brain iron levels may shed light on a possible role of iron deficiency in the pathophysiology of this "subtype" of ADHD [54].

A recent study in a sample of children with ADHD studied by means of video-polysomnography reported a relatively high frequency (11.9%) of leg discomfort at night associated with RLS, which is characterized by an overwhelming urge to move the legs, often accompanied by uncomfortable and unpleasant sensations. Moreover, the International RLS Rating Scale score, PLMS and PLMS during wake indexes correlated positively with the hyperactivity and opposition scores in the same sample of children [55].

In adults, research indicates that PLMS affect the quality of sleep and are associated with a shift to a relatively greater sympathetic influence over cardiovascular variables. A recent study found vagal inhibition associated with episodes of PLMS in children, thus indirectly confirming the same pattern in children [56]. Another studied reported that PLMS in children are independently associated with higher blood pressure indexes, particularly at night [57]. As all these data point to an increase in sympathetic activity during sleep, we may hypothesize that children with RSL and/or PLMS have an increased level of arousal during sleep.

For the same reasons as those provided in the case of children with the ADHD and OSAS sleep phenotype, we suggest that stimulant treatment should be avoided in children with ADHD symptoms and a diagnosis of RSL and/or PLMS, and that the main sleep disorders should be treated by means of iron supplements, dopaminergic stimulation, anticonvulsants, opiates and benzodiazepines [58].

Ictal and interictal epileptiform discharges (IEDs) during sleep in children with ADHD: varying level of arousal depending on whether the origin of the epileptiform discharges is focal or generalized

Many studies have demonstrated a relationship between IEDs during sleep (particularly centro-temporal and rolandic spikes) and neuropsychological dysfunction in children with language disorders, autism and ADHD [5]. The prevalence of interictal or ictal and IEDs was explored in a clinical sample of forty-two ADHD children who were referred to a sleep clinic for suspected sleep disorders and underwent a full-night video-PSG. The video-PSG revealed that a high percentage (53.1%) of ADHD children had IEDS of various types (28.2% had centro-temporal spikes, 12.5% frontal spikes, 9.3% temporal-occipital spikes and 2.3% generalized S-W). Nocturnal seizures were recorded in three patients: two with atypical interictal rolandic spikes and one with left frontal slow abnormalities [5]. These results were confirmed in a recent review in which one in four non-epileptic children who were examined on account of an attention deficit disorder had epileptiform discharges (more than half focal) displayed by sleep EEG recording and sleep-deprivation EEG recording. The majority of the EEG abnormalities (97.5%) occurred in the sleep and sleep-deprived recordings, with only 7% occurring in the prior wake recording; the highest prevalence of epileptiform discharges was observed in prolonged sleep recordings [59]. Furthermore, a neuropsychological assessment in children affected by benign epilepsy with centro-temporal or rolandic spikes (BECRS) and IEDs during sleep revealed disorders in visuospatial short-term memory, attention span, cognitive flexibility, verbal fluency, phonological awareness, visuoperceptual skills and academic performance, with a significant improvement following the remission of IEDs [60–63]. Memory strategy and complex motor planning impairments have been observed in children with frontal lobe epilepsy, with a greater severity being reported in children in whom epilepsy onset occurs at an early age. Children with frontal lobe epilepsy manifest more problems than those with temporal lobe epilepsy in planning, impulse control, verbal fluency, motor coordination and executive functions, though the former have better memory performances. A wide range of untreated cognitive, linguistic and behavioral-emotional co-morbidities have also been reported in childhood absence epilepsy [7]. Furthermore, other population studies have shown that ADHD and childhood epilepsy are often associated, with data ranging from 12% to 17% [6], and that epilepsy appears to be more severe in children who also have ADHD [64]. The interaction between EEG synchronizing events during sleep and EEG discharges may explain the relationship between cognitive deficit and epilepsy in children. The influence of epileptiform discharges on EEG sleep phasic events may underlie the cognitive impairment in epilepsy, even in the absence of associated seizures [7].

The influence of cyclic arousability and EEG synchrony on generalized interictal discharges has been studied by means of CAP analysis in primary generalized epilepsy and in lesional epilepsies with a frontotemporal focus. CAP analysis revealed increased NREM sleep instability, with a clear activation of interictal discharges, particularly in phase A, and a marked inhibition in phase B [65]. By contrast, a reduced total CAP rate, particularly in sleep stage N2, and reduced slow EEG slow oscillations and arousals in stages N1 and N2 have been reported in children with benign epilepsy characterized by rolandic spikes (BERS) [66]. Similar findings have been observed in a group of children with OSAS and IEDs (most of which occurred in the same regions as BERS) compared with children with OSAS without IEDs [67].

We may assume that children with ADHD and interictal or ictal IEDS display increased or decreased levels of arousal, depending on the type of discharges during sleep and of epilepsy, and that their sleep arousability patterns are altered.

Although stimulants remain the mainstay of pharmacotherapy for ADHD, such drugs may reduce the seizure threshold in children with co-morbid epilepsy, especially in cases in which the epilepsy is not well controlled. Although this risk is still a matter of debate [68,69], we believe that antiepileptic drugs should be the first-line treatment in this sleep phenotype of ADHD, and that those with a positive effect on vigilance and cognitive performance, such as lamotrigine, should be preferred. Although the results of a study designed to investigate the effects of psychostimulants (methylphenidate and dexamphetamine) in children with ADHD without epilepsy by means of standard EEG during wakefulness demonstrated the resolution of the electroencephalographic abnormalities (theta activity over frontal regions), the effects of stimulant treatment on interictal IEDS in children with ADHD remains unknown.

There are as yet few data regarding the effects of antiepileptic drugs on attention deficit and hyperactivity disorder symptoms in children who also have IEDS. A recent preliminary open-label study, conducted on a small sample of seven children with a complex co-morbidity involving ADHD, RLS and focal interictal epileptic discharges, reported that Levetiracetam had a positive effect on the children's sleep pattern and reduced their RLS symptoms [70].

Discussion

According to the sleep phenotypes of ADHD described above, treatment with stimulants appears to be indicated exclusively in the primary form of ADHD, i.e. the form not associated with either major sleep disorders or epileptiform discharges during sleep and/or epilepsy (ruled out by the clinical history and polysomnographic investigation), which are instead likely to be largely related to genetic conditions. In non-primary forms of ADHD, treatment should focus on the underlying sleep disorders (sleep onset insomnia,

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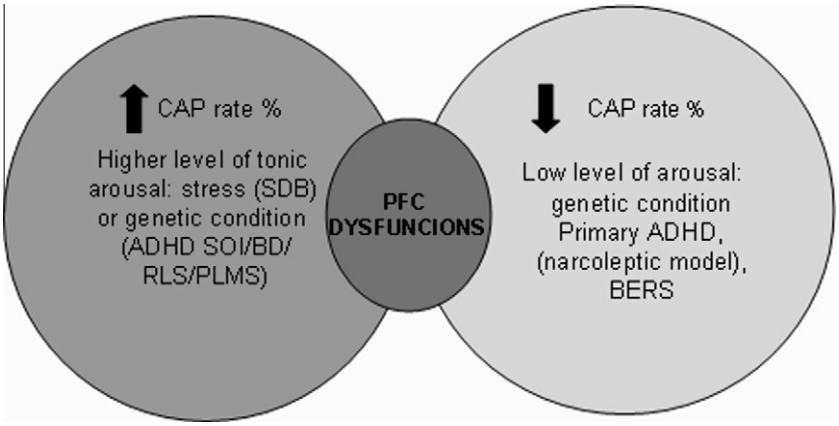

Fig. 1. Interactions between different levels of arousal during sleep and sleep phenotypes of ADHD. CAP: cyclic alternating pattern; ADHD: attention deficit hyperactivity disorders; SOI: sleep onset insomnia; BD: bipolar disorder; RLS: restless legs syndrome, PLMS: periodic limb movements; PFC: prefrontal cortex; BERS: benign epilepsy with rolandic spikes.

restless legs syndrome and/or periodic limb movements during sleep, obstructive sleep apnea syndrome) as well as on co-morbidities (i.e. epilepsy or bipolar disorders).

Moreover, we hypothesize different alterations of the arousal system during sleep related to each sleep phenotype. These alterations consist of an increased level of arousal in the majority of cases and a decreased level in the sleep phenotypes related to focal benign epilepsy, to focal IEDs and to the "primary" form of ADHD. One question that has yet to be answered is why the contrasting levels of arousal during sleep (which are also expressed by increased or decreased CAP rates during NREM sleep induce the same diurnal consequences as ADHD. We attempt to explain this apparent discrepancy below.

Some research indicates that there is a delay in cortical maturation in patients with ADHD. Indeed, Shaw et al. [71] demonstrated that children with ADHD reach the cortical thickness peak in the pre-frontal regions up to 2.5 years later than controls. Findings from imaging studies of ADHD point to volumetric differences in the prefrontal cortex (PFC), cerebellum and, possibly, the striatum [72], with the hallmark symptoms of ADHD reflecting a PFC dysfunction. Catecholamines generally exert a powerful effect on the local circuits of the PFC. The possible involvement of alterations in these circuits in the pathogenesis of ADHD is supported by recent research indicating that genetic changes in catecholamine pathways are associated with ADHD symptoms, and that the most effective treatments for ADHD act by enhancing the actions of catecholamines [73]. Numerous arousal systems, including the ascending monoamine systems (dopamine and norepinefrine), acetylcholine neurons from the basal forebrain and the more recently discovered orexins, project to the cortical mantle [74]. Both dopamine (DA) and norephinefrine (NE) exhibit an inverted U influence on PFC cognitive functions, with either too little or too much of these drugs impairing PFC function. Moderate NE levels improve PFC function by acting on postsynaptic α2A receptors, whereas high NE levels, such as those released during stress, impair working memory by acting on the α1 and β1 receptors [73]. As occurs in α2A receptor stimulation, moderate levels of D1 receptor stimulation are essential for PFC function, whereas high DA release levels (e.g. stress-induced) impair working memory. The PFC appears to thrive under conditions of moderate catecholamine release, in which NE α2A-receptor stimulation increases "signals," and optimal DA D1-receptor stimulation decreases "noise." By contrast, PFC working-memory functions are impaired by high catecholamine release levels, which engage the α1 and β receptors, and excessive D1-receptor stimulation [73]. Thus, catecholamines may act as a chemical switch, turning the PFC on during normal waking, and turning it off during stress. By contrast, high catecholamine levels may turn on more primitive brain structures, such as the amygdale, to achieve more automatic behavior control when exposed to danger. Drugs such as amphetamine, methylphenidate and atomoxetine enhance the release and/or inhibit the reuptake of both DA and NE, both of which are likely to be involved in the therapeutic effects of stimulants in patients with ADHD. However, excessive doses of stimulant medication may produce cognitive inflexibility through excessive α1-, β1- and D1-receptor stimulation [73]. This may be particularly problematic in children exposed to stressors such as families experiencing divorce, illness and death, or to social stressors at school. If the stressors are not identified, ADHD may be suspected and children may be treated inappropriately with stimulant medications that exacerbate their condition [73].

We suggest that major sleep disorders be considered as yet other forms of chronic stress, which increase tonic sympathetic activity, both during sleep and wakefulness. The link between prefrontal cortical activity, sleep and arousal has been explained in a recent review [75]. Moreover, functional MRI studies have recently demonstrated that NREM sleep cannot merely be defined as a state of global and regional brain activity decrease; rather, it appears to be an active state during which phasic increases in brain activity are synchronized with NREM sleep slow wave oscillations [76]. In particular, slow wave activation has been reported in both medial and inferior regions of the prefrontal cortex, which confirms previous findings from topographical scalp EEG studies [77,78], as well as arousal activation is reported in the brainstem nuclei located in the ponto-mesencephalic tegmentum, an area usually associated with arousal and awakening processes [79]. This area encompasses a major noradrenergic nucleus of the brainstem, the locus coeruleus (LC), whose neuronal activity has recently been shown to fire synchronously with cortical slow oscillation in rats [80]. In contrast to the classical view of brainstem nuclei promoting vigilance and wakefulness, these data suggest that several pontine structures, including the LC, might be active during NREM slow wave sleep, modulating cortical activity even during the deepest stages of sleep [75]. Slow wave oscillations during slow wave sleep are represented by the phasic events of cyclic alternating pattern (A subtypes), particularly by the A1 subtype, which mainly consist of slow waves and are mapped over frontal regions, particularly in the deepening sleep phases [41]. In conclusion, we believe that the sleep phenotypes related to ADHD express different levels of arousal, and consequently of CAP rate (low or high sleep arousability, low or high sleep NREM instability), but induce the same diurnal neurobehavioral effects. Both the increase and

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decrease in arousal reflect a reduced homeostatic process when neurobehavioral problems are expressed. Fig. 1 summarizes our hypothesis.

Conflict of interest statement

All authors are disclosing any affiliation, financial agreement, or other involvement of any author with any company whose product figures prominently in the submitted manuscript so that the editors can discuss with the affected authors whether to print this information and in what manner.

References

[1] Corkum P, Tannock R, Moldofsky H. Sleep disturbances in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1998;37:637–46.
[2] Owens JA. The ADHD and sleep conundrum: a review. J Dev Behav Pediatr 2005;26:312–22.
[3] Cortese S, Faraone SV, Konofal E, Lecendreux M. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. J Am Acad Child Adolesc Psychiatry 2009;48:894–908.
[4] Cortese S, Konofal E, Yateman N, Mouren MC, Lecendreux M. Sleep and alertness in children with attention-deficit/hyperactivity disorder: a systematic review of the literature. Sleep 2006;29:504–11.
[5] Silvestri R, Gagliano A, Calarese T, et al. Ictal and interictal EEG abnormalities in ADHD children recorded over night by video-polysomnography. Epilepsy Res 2007;75:130–7.
[6] Reilly CJ. Attention deficit hyperactivity disorder (ADHD) in childhood epilepsy. Res Dev Disabil 2011;32:883–93.
[7] Parisi P, Bruni O, Villa MP, et al. The relationship between sleep and epilepsy: the effect on cognitive functioning in children. Dev Med Child Neurol 2010;52:805–10.
[8] Gozal D. Obstructive sleep apnea in children: implications for the developing central nervous system. Semin Pediatr Neurol 2008;15:100–6.
[9] Kheirandish L, Gozal D. Neurocognitive dysfunction in children with sleep disorders. Dev Sci 2006;9:388–99.
[10] Lecendreux M, Konofal E, Bouvard M, Falissard B, Mouren-Simeoni MC. Sleep and alertness in children with ADHD. J Child Psychol Psychiatry 2000;41:803–12.
[11] Golan N, Shahar E, Ravid S, Pillar G. Sleep disorders and daytime sleepiness in children with attention-deficit/hyperactive disorder. Sleep 2004;27:261–6.
[12] Terzano MG, Parrino L. Origin and significance of the cyclic alternating pattern (CAP). Sleep Med Rev 2000;4:101–23.
[13] Terzano MG, Parrino L, Smerieri A, et al. Consensus Report. Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med 2001;2:537–53.
[14] Bruni O, Novelli L, Miano S, Parrino L, Terzano MG, Ferri R. Cyclic alternating pattern: a window into pediatric sleep. Sleep Med 2010;11:628–36.
[15] Miano S, Donfrancesco R, Bruni O, et al. NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. Sleep 2006;29:797–803.
[16] Ferri R, Miano S, Bruni O, et al. NREM-sleep alterations in narcolepsy/cataplexy. Clin Neurophysiol 2005;116:2675–84.
[17] Ferri R, Franceschini C, Zucconi M, et al. Sleep polygraphic study of children and adolescents with narcolepsy/cataplexy. Dev Neuropsychol 2009;34:523–38.
[18] Prihodova I, Paclt I, Kemlink D, Nevsimalova S. Sleep microstructure is not altered in children with attention-deficit/hyperactivity disorder (ADHD). Physiol Res 2011;61:125–33.
[19] Huang YS, Tsai MH, Guilleminault C. Pharmacological treatment of ADHD and the short and long term effects on sleep. Curr Pharm Des 2011;17:1450–8.
[20] Weiss MD, Salpekar J. Sleep problems in the child with attention-deficit hyperactivity disorder: defining aetiology and appropriate treatments. CNS Drugs 2010;24:811–28.
[21] Spruyt K, Gozal D. Sleep disturbances in children with attention-deficit/hyperactivity disorder. Expert Rev Neurother 2011;11:565–77.
[22] Van der Heijden KB, Smits MG, Van Someren EJ, Gunning WB. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: a circadian rhythm sleep disorder. Chronobiol Int 2005;22:559–70.
[23] Van der Heijden KB, Smits MG, Gunning WB. Sleep hygiene and actigraphically evaluated sleep characteristics in children with ADHD and chronic sleep onset insomnia. J Sleep Res 2006;15:55–62.
[24] Corkum P, Moldofsky H, Hogg-Johnson S, Humphries T, Tannock R. Sleep problems in children with attention-deficit/hyperactivity disorder: impact of subtype, comorbidity, and stimulant medication. J Am Acad Child Adolesc Psychiatry 1999;38:1285–93.
[25] Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D. Is comorbidity with ADHD a marker for juvenile-onset mania? J Am Acad Child Adolesc Psychiatry 1997;36:1046–55.
[26] Donfrancesco R, Miano S, Martines F, Ferrante L, Melegari MG, Masi G. Bipolar disorder co-morbidity in children with attention deficit hyperactivity disorder. Psychiatry Res 2011;186:333–7.
[27] Heiler S, Legenbauer T, Bogen T, Jensch T, Holtmann M. Severe mood dysregulation: in the "light" of circadian functioning. Med Hypotheses 2011;77:692–5.
[28] Staton D. The impairment of pediatric bipolar sleep: hypotheses regarding a core defect and phenotype-specific sleep disturbances. J Affect Disord 2008;108:199–206.
[29] Szeinberg A, Borodkin K, Dagan Y. Melatonin treatment in adolescents with delayed sleep phase syndrome. Clin Pediatr 2006;45:809–18.
[30] Bendz LM, Scates AC. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. Ann Pharmacother 2010;44:185–91.
[31] Ivanenko A, Johnson K. Sleep disturbances in children with psychiatric disorders. Semin Pediatr Neurol 2008;15:70–8.
[32] Findling RL, Youngstrom EA, McNamara NK, et al. Double-blind, randomized, placebo-controlled long-term maintenance study of aripiprazole in children with bipolar disorder. J Clin Psychiatry 2012;73:57–63.
[33] West AE, Weinstein SM, Celio CI, Henry D, Pavuluri MN. Co-morbid disruptive behavior disorder and aggression predict functional outcomes and differential response to risperidone versus divalproex in pharmacotherapy for pediatric bipolar disorder. J Child Adolesc Psychopharmacol 2011;21:545–53.
[34] Covassin N, de Zambotti M, Sarlo M, De Min Tona G, Sarasso S, Stegagno L. Cognitive performance and cardiovascular markers of hyperarousal in primary insomnia. Int J Psychophysiol 2011;80:79–86.
[35] Terzano MG, Parrino L, Spaggiari MC, Palomba V, Rossi M, Smerieri A. CAP variables and arousals as sleep electroencephalogram markers for primary insomnia. Clin Neurophysiol 2003;114:1715–23.
[36] Chervin RD, Ruzicka DL, Archbold KH, Dillon JE. Snoring predicts hyperactivity four years later. Sleep 2005;28:885–90.
[37] Chervin RD, Burns JW, Subotic NS, Roussi C, Thelen B, Ruzicka DL. Correlates of respiratory cycle-related EEG changes in children with sleep-disordered breathing. Sleep 2004;27:116–21.
[38] O'Brien LM, Gozal D. Sleep in children with attention deficit/hyperactivity disorder. Minerva Pediatr 2004;56:585–601.
[39] Kheirandish-Gozal L, de Jong MR, Spruyt K, Chamuleau SA, Gozal D. Obstructive sleep apnoea is associated with impaired pictorial memory task acquisition and retention in children. Eur Respir J 2010;36:164–9.
[40] Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioural deficits. J Sleep Res 2002;11:1–16.
[41] Ferri R, Bruni O, Miano S, Terzano MG. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). Sleep Med 2005;6:29–36.
[42] Guilleminault C, Lee JH, Chan A, Lopes MC, Huang YS, da Rosa A. Non-REM-sleep instability in recurrent sleepwalking in pre-pubertal children. Sleep Med 2005;6:515–21.
[43] Lopes MC, Guilleminault C. Chronic snoring and sleep in children: a demonstration of sleep disruption. Paediatrics 2006;118:e741–6.
[44] Kheirandish-Gozal L, Miano S, Bruni O, Ferri R, Pagani J, Villa MP. Reduced NREM sleep instability in children with sleep disordered breathing. Sleep 2007;30:450–76.
[45] Miano S, Rizzoli A, Evangelisti M, Bruni O, Ferri R, Villa MP. NREM sleep instability changes following rapid maxillary expansion in children with obstructive apnea sleep syndrome. Sleep Med 2009;10:471–8.
[46] Miano S, Paolino MC, Urbano A, et al. Neurocognitive assessment and sleep analysis in children with sleep-disordered breathing. Clin Neurophysiol 2011;122:311–9.
[47] Muzumdar HV, Sin S, Nikova M, Gates G, Kim D, Arens R. Changes in heart rate variability after adenotonsillectomy in children with obstructive sleep apnea. Chest 2011;139:1050–9.
[48] Montesano M, Miano S, Paolino MC, et al. Autonomic cardiovascular tests in children with obstructive sleep apnea syndrome. Sleep 2010;33:1349–55.
[49] Abdel-Wahab BA, Abd El-Aziz SM. *Ginkgo biloba* protects against intermittent hypoxia-induced memory deficits and hippocampal DNA damage in rats. Phytomedicine 2012;19:444–50.
[50] Silberstein RB, Pipingas A, Song J, Camfield DA, Nathan PJ, Stough C. Examining brain-cognition effects of *Ginkgo biloba* extract: brain activation in the left temporal and left prefrontal cortex in an object working memory task. Evid Based Complement Alternat Med 2011;2011:164139.
[51] Donfrancesco R, Ferrante L. *Ginkgo biloba* in dyslexia: a pilot study. Phytomedicine 2007;14:367–70.
[52] Salehi B, Imani R, Mohammadi MR, et al. *Ginkgo biloba* for attention-deficit/hyperactivity disorder in children and adolescents: a double blind, randomized controlled trial. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:76–80.
[53] Pockett C, Kirk V. Periodic limb movements in sleep and attention deficit hyperactivity disorder: are they related? Paediatr Child Health 2006;11:355–8.
[54] Cortese S, Azoulay R, Castellanos FX, et al. Brain iron levels in attention deficit/hyperactivity disorder: A pilot MRI study. World J Biol Psychiatry 2011;13:223–31.
[55] Silvestri R, Gagliano A, Aricò I, et al. Sleep disorders in children with Attention-Deficit/Hyperactivity Disorder (ADHD) recorded overnight by video-polysomnography. Sleep Med 2009;10:1132–8.
[56] Walter LM, Foster AM, Patterson RR, et al. Cardiovascular variability during periodic leg movements in sleep in children. Sleep 2009;32:1093–9.
[57] Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. Sleep 2010;33:759–65.

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[58] Frenette E. Restless legs syndrome in children: a review and update on pharmacological options. Curr Pharm Des 2011;17:1436–42.
[59] Millichap JG, Millichap JJ, Stack CV. Utility of the electroencephalogram in attention deficit hyperactivity disorder. Clin EEG Neurosci 2011;42:180–4.
[60] Baglietto MG, Battaglia FM, Nobili L, et al. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes Benign epilepsy. Dev Med Child Neurol 2001;43:407–12.
[61] Lindgren A, Kihlgren M, Melin L, Croona C, Lundberg S, Eeg-Olofsson O. Development of cognitive functions in children with rolandic epilepsy. Epilepsy Behav 2004;5:903–10.
[62] Northcott E, Connolly AM, Berroya A, et al. Memory and phonological awareness in children with Benign Rolandic Epilepsy compared to a matched control group. Epilespy Res 2007;75:57–62.
[63] Piccinelli P, Borgatti R, Aldini A, et al. Academic performance in children with rolandic epilepsy. Dev Med Child Neurol 2008;50:353–6.
[64] Davis SM, Katusic SK, Barbaresi WJ, et al. Epilepsy in children with attention-deficit/hyperactivity disorder. Pediatr Neurol 2010;42:325–30.
[65] Parrino L, Smerieri A, Terzano MG. Combined influence of cyclic arousability and EEG synchrony on generalized interictal discharges within the sleep cycle. Epilepsy Res 2001;44:7–18.
[66] Bruni O, Novelli L, Luchetti A, et al. Reduced NREM sleep instability in benign childhood epilepsy with centro-temporal spikes. Clin Neurophysiol 2010;121:665–71.
[67] Miano S, Paolino MC, Peraita-Adrados R, Montesano M, Barberi S, Villa MP. Prevalence of EEG paroxysmal activity in a population of children with obstructive sleep apnea syndrome. Sleep 2009;32:522–9.
[68] Koneski JA, Casella EB. Attention deficit and hyperactivity disorder in people with epilepsy: diagnosis and implications to the treatment. Arq Neuropsiquiatr 2010;68:107–14.
[69] Parisi P, Moavero R, Verrotti A, Curatolo P. Attention deficit hyperactivity disorder in children with epilepsy. Brain Dev 2010;32:10–6.
[70] Gagliano A, Aricò I, Calarese T, et al. Restless Leg Syndrome in ADHD children: levetiracetam as a reasonable therapeutic option. Brain Dev 2011;33:480–6.
[71] Shaw P, Eckstrand K, Sharp W, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci USA 2007;104:19649–54.
[72] Giedd JN, Blumenthal J, Molloy E, Castellanos FX. Brain imaging of attention deficit/hyperactivity disorder. Ann NY Acad Sci 2001;931:33–49.
[73] Brennan AR, Arnsten AF. Neuronal mechanisms underlying attention deficit hyperactivity disorder: the influence of arousal on prefrontal cortical function. Ann NY Acad Sci 2008;1129:236–45.
[74] Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biol Psychiatry 2005;57:1377–84.
[75] Dang-Vu TT, Schabus M, Desseilles M, Sterpenich V, Bonjean M, Maquet P. Functional neuroimaging insights into the physiology of human sleep. Sleep 2010;33:1589–603.
[76] Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 2000;9:207–31.
[77] Finelli LA, Borbely AA, Achermann P. Functional topography of the human nonREM sleep electroencephalogram. Eur J Neurosci 2001;13:2282–90.
[78] Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. The sleep slow oscillation as a traveling wave. J Neurosci 2004;24:6862–70.
[79] Steriade M, McCarley RW. Brain control of wakefulness and sleep. New York: Springer; 2005.
[80] Yeshenko O, Moelle M, Marshall L, Born J, Sara SJ. Locus coeruleus firing during SWS is time locked to slow oscillations: possible contribution of the noradrenergic system to off-line information processing in rats. J Sleep Res 2006;15:11.

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