Sleep microstructure is not altered in children with attention-deficit/hyperactivity disorder (ADHD)

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Short title: Sleep microstructure in ADHD

Summary: *Objective:* The high rate of occurrence of sleep disturbances in children with attention-deficit/hyperactivity disorder (ADHD) prompted the idea that structural and neurotransmitter changes might give rise to specific sleep pattern abnormalities. The aim of this study was to evaluate the microstructure of sleep in children with ADHD who had no polysomnographically diagnosed sleep disorder, had never been treated for ADHD, and were free from any psychiatric comorbidity. *Participants and methods:* 14 patients with ADHD (12 boys and 2 girls aged 7–12 years, mean age 9.6 ± 1.6). ADHD was diagnosed according to DSM-IV criteria (Diagnostic and statistical manual of mental disorders). Psychiatric comorbidities were ruled out by detailed psychiatric examination. The patients underwent two consecutive overnight video-polysomnographic (PSG) recordings, with the sleep microstructure (cyclic alternating pattern–CAP) scoring during the second night. The data were compared with age- and sex-matched controls. *Results:* Sleep microstructure analysis using CAP revealed no significant differences between the ADHD group and the controls in any of the parameters under study. *Conclusion:* No ADHD-specific alterations were found in the sleep microstructure.

Key words: attention-deficit/hyperactivity disorder, nocturnal video-polysomnography, cyclic alternating pattern

Introduction

Affecting some 4–12% of children, attention-deficit/hyperactivity disorder (ADHD) is is the most frequent neurobehavioral disorder in that particular age bracket (Biederman and Faraone 2005). To go by parental data, sleep disorders in children with ADHD occur at a rate of 50-60% (Corkum et al. 1998, Owens et al. 2000), indeed, they used to be part of the diagnostic criteria for ADHD (American Psychiatric Association 1980). The assumption was that

neurotransmitter and structural changes underlying ADHD might also underlie changes in the sleep structure and sleep disturbances (O´Brien and Gozal 2004). However, as follows from reviews and meta-analytic studies, there is no convincing proof of any consistent ADHD-specific changes in the duration of sleep or in the sleep macrostructure (Cohen-Zion and Ancoli-Israel 2004, Sadeh et al. 2006, Cortese et al. 2006, 2009). The latter, however, fails to provide complete information for rating the quality and function of sleep. In some sleep disorders (obstructive sleep apnea–OSA, periodic limb movements in sleep–PLMS) the macrostructure remains unaltered in the presence of a number of daytime manifestations arising from fragmented sleep (Bonnet et al. 1989, 2003). The microstructure is reflected in the number of arousals as it signals the degree of sleep disturbance and correlates with daytime complaints (Roehrs et al. 1989). Sleep microstructure analysis is important especially in children. Arousals and changes in sleeep macrostructure are less frequent than in adults due to a higher arousal threshold (NcNamara et al.1996, Scholle et al. 2001, O´Brien et al. 2004). Comprehensive microstructure rating facilitates the determination of cyclic alternating pattern (CAP) events (Terzanno et al. 2001) which are seen as a sensitive indicators of sleep fragmentation in children (Bruni et al. 2002, Ferri et al. 2005).

The purpose of our effort was to study the microstructure of sleep by means of CAP after the inclusion of an adaptation night in a group of children with ADHD yet without any concurrent sleep disorder or psychiatric comorbidities, and never treated for ADHD before.

Participants and methods

Participants

The cohort was made up of 14 children (12 boys and 2 girls aged 7–12 years, mean age 9.6 ± 1.6), participants in a previous study (Prihodova et al. 2010), who had no sleep disorder revealed during nocturnal video-polysomnography (PSG). All were

enrolled in the study before the start of medication for ADHD. The enrollment criteria were as follows: 1) ADHD diagnosed on the basis of DSM-IV (American Psychiatric Association 1994), 2) no previous pharmacological treatment for ADHD, 3) no history of any chronic physical condition (including obesity), chronic sleep disorder, neurological or other psychiatric disorders (including mental retardation and autism) based on a complete pediatric report and on neurological and psychiatric examination, 4) no current medication (psychotropic or general), 5) the patient´s and his/her parents´ willingness to participate in the study and informed consent signed by the parents.

The cohort underwent psychological, psychiatric and neurological testing. The diagnosis of ADHD was established by means of a detailed clinical interview which included a structured psychiatric examination - Children´s Psychiatric Rating Scale (Fish 1985) and DSM-IV diagnostic criteria for ADHD (American Psychiatric Association 1994). These criteria were also used for the classification of ADHD subtypes. A combined type of ADHD was predominant (12 patients), 2 had an inattentive type of ADHD. The Conners´ Parent Rating Scale (Conners 1997) was also employed to assess the severity of ADHD symptoms (a score of at least 2 SD above the mean on this scale and ADHD index were used to classify the children as having significant ADHD symptoms). To forestall any emotional and behavioral problems, the following additional tools were employed: Child Behavior Checklist for parents, Children´s Manifest Anxiety Scale and Children´s Depression Inventory.

The control group was made up by 12 children (8 boys, 4 girls, age range 7–12 years, mean age 9.0 ± 1.6) who had likewise participated in the previous study and in whom no sleep disorder was revealed during nocturnal PSG. The had no chronic morbidity and used no medication. The diagnosis of ADHD was ruled out according to DSM-IV criteria. The

Conners´ Parent Rating Scale and Child Behavior Checklist were also administered. The results of psychiatric scales are summarized in Table 1.

Methods

Children with ADHD and the controls had nocturnal PSG performed for 2 consecutive nights in the sleep laboratory. The first one was rated as an adaptation night. A Schwarzer polygraph was used for all PSG studies with electroencephalographic (EEG) montage (F4-C4, C4-P4, F3-C3, C3-P3, C4-A1, C3-A2), horizontal electrooculography, submental and bilateral anterior tibialis electromyography, electrocardiography and videorecording using an infrared-light camera. This type of EEG montage was used in our laboratory to allow detection of epileptiform discharges in children. Oronasal airflow was monitored with thermistors. Thoracic and abdominal respiratory movements were recorded using belts with piezosensors. Respiratory sounds were microphone-monitored. Oxyhemoglobin saturation was measured using pulse oximetry (Schwarzer EPAS 32). Neither esophageal pressure measurement nor a nasal cannula/presssure transducer were used. The nasal cannula/presssure transducer offers a more accurate method for the evaluation of subtler forms of sleep disordered breathing, i.e.for the detection of the upper airway resistance syndrome.

The second-night record was used for scoring. The sleep stages were visually scored according to the Rechtschaffen and Kales standard criteria in 30-second epochs (Rechtschaffen and Kales 1968). Conventional sleep parameters (total sleep time, sleep efficiency, sleep-onset latency, rapid eye movement sleep latency, percentage of sleep stages, movement time) were evaluated. Apneas and hypopneas were scored to determine the apnea index (AI) and the apnea-hypopnea index (AHI) (American

Thoracic Society 1996). AHI>1 was considered abnormal relative to normative data in children (Marcus et al. 1992). Periodic limb movements (PLM) were scored according to standard International classification of sleep disorders (ICSD-2) criteria (American Academy of Sleep Medicine 2005). The periodic limb movement index (PLMI) was calculated as the number of PLM per hour of sleep. As a cut-off for abnormality we chose PLMI>5, a value generally considered abnormal in children (American Academy of Sleep Medicine 2005).

Each sleep record was transformed into the EDF format, converted and rated with Somnologica TM, Flaga-Medcare, Iceland, a software which enables visual scoring of phase-A subtypes. The text file with the results was exported and processed by a software HypnoLab vers.1.2.177, SWS-Soft which automatically analyses CAP parameters.

CAP was scored following the criteria published by Terzanno et al (Terzanno et al. 2001).

CAP is a periodic EEG activity during non rapid eye movement (NREM) sleep characterized by repeated spontaneous sequences of transient events (phase A), whose frequency and amplitude differ from the background activity of that sleep stage (the amplitude should be one third higher than that recorded in the preceding 2 seconds). Return to the background activity is called phase B. Each phase lasts 2 to 60 seconds. Phase A and B together form a CAP cycle. The presence of at least two CAP cycles following one another adds up to a CAP sequence. The absence in the graph of any signs of CAP for longer than 60 seconds is described as non-CAP.

Phase A is divided into 3 subtypes reflecting different level of the arousal during NREM sleep (Fig. 1,2).

A1–predominantly synchronized EEG pattern (intermittent alpha rhythm in NREM 1 sleep, vertex waves, K-complex sequences, delta bursts, polyphasic bursts of slow and fast rhythms in the other sleep stages), containing less than 20% of desynchronized activity.

A2–partially desynchronized pattern with slow high-voltage activity followed by fast low-voltage aktivity (K-complex with alpha or beta activities, polyphasic burts) associated with moderate autonomous system activation (increase of muscle tone, cardiorespiratory rate), contains 10-50% of desynchronized activity.

A3–desynchronized pattern with remarkable autonomous system activation; more than 50% is made up of fast, low-amplitude rhythms, such as K-alpha complexes, arousals, polyphasic bursts.

The following CAP parameters were determined: CAP time (a sum of all CAP sequences), CAP rate (NREM sleep percentage formed by CAP sequences), number and duration of CAP cycles, number and duration of CAP sequences, number, duration and percentage of phase A (including subtypes), A1 index (number of A1 subtypes per hour of NREM sleep), A2 index (number of A2 subtypes per hour of NREM), A3 index (number of A3 subtypes per hour of NREM), number and duration of phase B.

Statistics

The two basic statistical chararacteristics, mean values and standard deviations, were calculated for each quantitative quality. The unpaired two-sample t-test (Student´s test) was employed for testing the mean value differences between the ADHD group and the controls. Despite the fact, that minority of data (2 parameters out of CAP set, and those naturally not normally distributed–AHI a PLMI) were not normally distributed (as shown by Kormogolov-Smirnov test in controls), we preferred parametric test over non-parametric in order to allow further power analyses. Non-parametric comparisons were performed using Mann-Whitney's

test. These statistical analyses were performed using STATISTICA version 10 (Statsoft, USA).

Cohen's d was calculated to demonstrate effect sizes in individual parameters using a web-based calculator (http://www.uccs.edu/~faculty/lbecker/).

Results

Comparisons of the sleep macrostructure (Tab. 2) and microstructure (Tab. 3) revealed no differences between the two groups between the two groups by means of both Student´s and Mann-Whitney's test respectively of normality of distribution and violation of t-test assumptions. We did not find any changes in CAP rate, CAP time or CAP subtypes distribution between both investigated groups.

Discussion

Most PSG studies stop short of corroborating parental information about prolonged sleep-onset latency, recurrent nocturnal awakenings, shortened or variable sleep duration, nor have any deviations been found in the macrostructure of sleep (or else, individual studies have produced markedly heterogeneous if not contradictory results). Hence, the current endeavour to find an ADHD-specific sleep disorder is aimed at the microstructure of sleep.

The CAP rate is seen as a physiological indicator of sleep stability and as an expression of sleep quality (Terzanno et al. 2000) correlating with subjective sleep quality rating – the higher the CAP rate, the worse the quality of sleep (Terzanno et al. 1990). The CAP rate is increased in different sleep disorders (insomnia, PLMS, OSA), and rises physiologically with age. The reference value in schoolchildren is 33%, in the elderly up to 45% (Parrino et al. 1998). During the night, the CAP rate increases as sleep becomes deeper. The highest values

are found in delta sleep with a growing share of mainly subtype A1. This subtype is coresponsible for the maintetance of deep sleep, representing the least variability in the level of arousal. It reflects the brain´s successful effort to maintain NREM sleep despite potential internal and external arousal stimuli activating the reticular formation. When this effort fails, subtypes A2 or A3 appear in what is an arousal reaction. In this way, the sleep microstructure flexibility makes for a stable macrostructure (Terzanno et al. 2000).

Comprehensive sleep microstructure evaluation with CAP in children with ADHD has so far appeared in only one study, the results of which support the hypothesis of impaired control of vigilance and arousal mechanisms in ADHD. Using a cohort of 20 children with a predominantly mixed type of ADHD, Miano et al. 2006 found a significant reduction of the CAP rate. Their finding pertained solely to subtype A1 which was reduced and lasted longer in superficial sleep (NREM 1 and 2). Children with ADHD also had fewer CAP sequences and shortened total sleep time. The authors speculate that chronic partial sleep deprivation in children with ADHD ultimately increases homeostatic sleep pressure, thus reducing the CAP rate. In their view, A1 reduction in NREM 2 sleep is an ADHD-specific finding. Comparing those findings with narcoleptic patients, they see them as an abnormity of arousal mechanisms.

In our study of children with ADHD we found no significant differences in any of the CAP parameters. As for the microstructure of sleep, we could not corroborate the hypothesis of chronic sleep deprivation in children with ADHD or of a disorder of arousal mechanisms.

The cause of this discrepancy between our own and the Miano et al. 2006 study is unclear. The interpretation of a lower occurrence of subtype A1 in superficial sleep is not quite consistent, because already in delta sleep the share of A1 was within norm. Nor is it clear why a change in the stability of sleep should selectively comprise NREM 1/2 phases and not also synchronous sleep with its predominance of the A1 phase. Indeed, a recent study by Silvestri

et al. 2009 carries evidence of an increased number of arousals in children with ADHD who, relative to CAP scoring, have an equivalent in subtypes A2 and A3.

The differences in the outcome of our study may also lie in the variability of CAP scoring. Unlike the scoring of the macrostructure of sleep where congruence is very likely, the scoring of sleep microstructure parameters (arousals) may differ from centre to centre (Bonnet et al. 2007). Evidence of this inter-centre variability can be read from works by Bruni et al. 2002 and Lopez et al. 2005, who studied CAP in healthy, age-matched children and who arrived at markedly different results. Bruni et al. 2002, found a CAP rate of 33% in a group aged 6–10 years, while Lopez et al. 2005, calculated a rate of 65% in a cohort of children aged 8–12 years.

Even though Ferri et al. 2005 revealed inter-centre agreement in the scoring of the basic parameters of CAP, in a detailed analysis (shares of different subtypes in sleep stages and their duration) this agreement was already less expressed. Another potential limitation of our study may represent the relatively small sample size .

Conclusion

Having studied previously untreated children free from psychiatric comorbidities and sleep disorders, we found no specific changes in their sleep microstructure. Our findings do not support the theory of chronic sleep deprivation in children with ADHD or of impaired control of vigilance and arousal mechanisms. This discrepance between our findings and the only present-day study of that particular aspect calls for more research using larger cohorts to verify the results.

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Table 1. Characteristics of participants: results of psychiatric scales

Psychiatric scale	ADHD (n=14)	Controls (n=12)	P value
CPRS Global index total	77.5 ± 13.9	45.8 ± 4.5	p<0.001
ADHD index	84.1 ± 15.8	43.2 ± 1.8	p<0.001
CBCL total	72.1 ± 16.9	45.9 ± 8.5	p<0.001

T-scores are provided. Data are presented as mean ± standard deviation
CPRS–Conners´ Parent Rating Scale, ADHD–attention-deficit/hyperactivity disorder, CBCL–Child Behavior Checklist

Table 2. Polysomnographic parameters

Sleep parameters	ADHD (n=14)	Controls (n=12)	P value	Cohen's d
Sleep onset latency (min)	13.9 ± 9.0	11.5 ±6.3	ns	0.31
REM sleep latency (min)	99.7 ± 37.6	92.9 ± 49.9	ns	0.15
Total sleep time (min)	530.4 ± 27.1	520.3 ± 36.6	ns	0.31
Sleep efficiency (%)	95.1 ± 2.7	91.2 ± 5.1	ns	0.96
Wakefulness (%)	2.3 ± 2.2	3.1 ± 2.3	ns	0.36
NREM 1 (%)	2.2 ± 2.6	1.6 ± 1.1	ns	0.30
NREM 2 (%)	44.8 ± 4.8	44.3 ± 5.3	ns	0.10
NREM 3,4 (%)	24.5 ± 3.7	26.6 ± 3.4	ns	0.57
REM (%)	25.6 ± 4.0	24.0 ± 3.3	ns	0.44
Movement time (%)	0.5 ± 1.0	0.4 ± 0.3	ns	0.14
AHI	0.7 ± 0.4	0.8 ± 0.7	nn	0.18
AI	0.4 ± 0.3	0.5 ±0.3	nn	0.33
PLMI	1.1 ± 1.6	2.0 ± 4.0	nn	0.26

REM–rapid eye movement, NREM–non rapid eye movement, AHI–apnea hypopnea index, AI–apnea index, PLMI–periodic limb movement index, ns–nonsignificant, nn–not normally distributed and also nonsignificant

The data are given as mean ± standard deviation

Table 3. CAP parameters

CAP parameters	ADHD (n=14)	Controls (n=12)	P value	Cohen's d
CAP rate NREM (%)	34.7 ± 6.7	33.8 ± 5.9	ns	0.14
NREM 1	20.4 ± 21.4	12.2 ± 16.1	ns	0.43
NREM 2	22.4 ± 8.4	25.4 ± 7.0	ns	0.19
NREM3/4	47.3 ± 11.7	40.1 ± 10.4	ns	0.31
CAP time (min)	135.0 ± 29.4	131.1 ± 28.9	ns	0.07
Number of CAP cycles	394.0 ± 61.5	378. 6 ± 73.5	ns	0.11
A1 (%)	78.2 ± 5.0	79.4 ± 3.6	ns	0.14
A2 (%)	15.1 ± 5.0	14.6 ± 2.7	ns	0.06
A3 (%)	6.7 ± 2.9	6.0 ± 2.1	ns	0.14
A1 index (no/h)	40.0 ± 7.0	39.2 ± 9.1	ns	0.16
NREM 1	8.2 ±11.0	5.1 ± 4.2	ns	0.37
NREM 2	28.0 ± 8.7	32.0 ± 9.2	ns	0.47
NREM 3/4	68.1 ± 16.2	58.7 ± 15.3	ns	0.60
A2 index (no/h)	7.5 ± 3.2	6.9 ± 1.8	ns	0.15
NREM 1	4.7 ± 10.8	4.3 ± 6.5	ns	0.05
NREM 2	11.8 ± 4.6	11.5 ± 2.5	ns	0.08
NREM 3/4	4.9 ± 1.8	3.7 ± 2.0	ns	0.63
A3 index (no/h)	2.9 ± 1.6	2.2 ± 1.0	ns	0.52
NREM 1	24.3 ± 18.9	15.6 ± 16.4	ns	0.49
NREM 2	5.0 ± 2.3	4.4 ± 1.2	ns	0.33
NREM3/4	0.7 ± 0.7	0.7 ± 0.7	ns	0
A mean duration (sec)	6.9 ± 0.7	7.9 ± 1.9	ns	0.70
A1 mean duration (sec)	5.2 ± 0.6	5.8 ± 1.3	ns	0.59
NREM 1	1.7 ± 2.6	1.6 ± 3.3	nn	0.03
NREM 2	5.0 ± 0.7	5.6 ± 1.2	ns	0.61
NREM 3/4	5.4 ± 0.8	6.3 ± 1.6	ns	0.71
A2 mean duration (sec)	11.7 ± 2.0	14.2 ± 5.1	ns	0.67
NREM 1	3.5 ± 6.0	7.6 ± 12.1	ns	0.42
NREM 2	10.3 ± 1.5	12.9 ± 3.9	ns	1.10
NREM 3/4	18.1 ± 5.5	20.6 ± 10.0	ns	0.31
A3 mean duration (sec)	16.4 ± 2.9	20.8 ± 6.8	ns	0.84
NREM 1	8.1 ± 5.4	9.7 ± 7.0	ns	0.26
NREM 2	16.6 ± 2.9	20.5 ± 6.0	ns	0.83
NREM 3/4	19.6 ± 14.2	23.2 ± 22.8	ns	0.19
B mean duration (sec)	22.1 ± 1.5	22.1 ± 4.1	ns	0

Cycle mean duration (sec)	28.8 ± 1.7	29.8 ± 3.1	ns	0.36
CAP sequences (no)	40.2 ± 4.7	38.9 ± 7.2	ns	0.20
Sequence mean duration (sec)	204.3 ± 35.1	206.8 ± 27.0	ns	0.08
Number of cycles in sequence	8.1 ± 1.2	8.0 ± 1.4	ns	0.08

The data are given as mean ± standard deviation

CAP–cyclic alternating pattern, NREM– non rapid eye movement

ns–nonsignificant, nn–not normally distributed and also nonsignificant

Figure 1. CAP – examples of subtypes A1 and A2 (page 60 seconds)

Channels are from top to bottom: EEG (electroencephalogram) leads: F3-C3, C3-A2, C3-P3, C4-A1, C4-P4, F4-C4, EOG (horizontal electrooculogram), EMG (chin electromyogram)

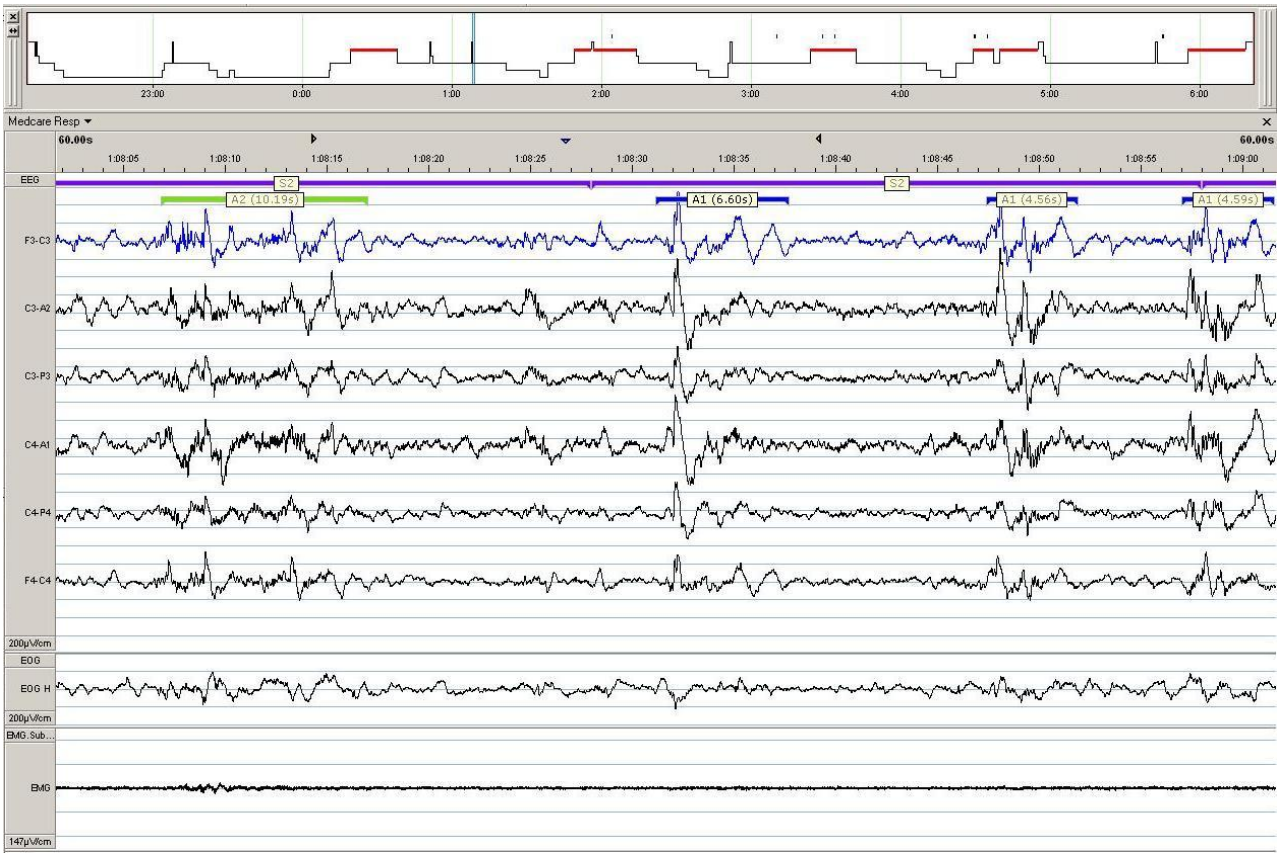

Figure 2. CAP – example of subtype A3 (page 60 seconds)

Channels are from top to bottom: EEG (electroencephalogram) leads: F3-C3, C3-A2, C3-P3, C4-A1, C4-P4, F4-C4, EOG (horizontal electrooculogram), EMG (chin electromyogram)