Network Analysis on Overnight EEG Spectrum to Assess Relationships Between Paediatric Sleep Apnoea and Cognition

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Abstract. One major risk of paediatric sleep apnoea-hypopnoea syndrome (SAHS) is the development of cognitive impairments among affected children. Electroencephalography (EEG) is ordinarily used as part of polysomnography, the standard diagnostic test for SAHS. However, how SAHS changes overnight EEG, and its relationships with cognitive performance, remains unclear. In this study, we first analyzed the spectral content of EEG recordings from 294 children to explore possible differences caused by SAHS. Then, a correlation network analysis was conducted to evaluate relationships among different EEG spectral bands and the results from the Differential Ability Scales (DAS) battery of cognitive tests. Our analyses identified up to six new SAHS spectral bands of interest in the EEG. They also showed higher absolute correlations among the different spectral bands as SAHS severity increased. Higher SAHS severity degree also indicated higher absolute correlations with DAS tests. Our results suggest that the spectral content of the overnight EEG is useful to characterize both paediatric SAHS and the cognitive performance of the affected children.

Keywords: Paediatric sleep apnoea · EEG · Spectral analysis · Correlation networks

1 Introduction

The sleep apnoea-hypopnoea syndrome (SAHS) is a highly prevalent disease affecting up to 5% of children [1]. Recurrent upper airway collapse and airflow reductions during the night lead to inadequate gas exchange, hypoxia episodes and fragmented sleep [2]. These undesirable effects may cause negative symptoms among which cognitive and behavioral deficits are regarded as very common and deleterious [2].

Several previous studies focused on establishing relationships between paediatric SAHS and the cognitive performance of affected children. These studies provided evidence of higher prevalence of SAHS among poorly performing students [3],

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associations between SAHS symptoms and lower cognitive functioning [4], as well as relationships between SAHS presence/severity and lower scoring in neurocognitive tests [2, 5]. Additionally, recent studies have focused on specific electroencephalographic (EEG) events, reaching different conclusions about associations between slow waves and spindle patterns with SAHS and cognition [6, 7]. Although EEG is ordinarily used to evaluate sleep architecture, its overnight analysis in healthy and SAHS-affected children has been scarcely investigated. Hence, in this preliminary study, we propose the analysis of the entire overnight EEG.

Spectral analysis has shown its usefulness in different contexts to automatically process biomedical signals, such as EEG [8] and magnetoencephalography (MEG) [9], including overnight recordings associated with SAHS [10–12]. The recurrent nature of the apneic events, which also induce abnormal recurrent episodes in the EEG, such as respiratory arousals [13], also supports the suitability of this frequency-domain methodology. Accordingly, we hypothesized that the spectral information of the overnight EEG provides useful information about paediatric SAHS and its cognitive implications.

In order to evaluate this assumption, we calculated the relative power (RP) from the conventional EEG frequency bands, as well as from new SAHS-related bands of interest (BOI) identified during the current study. RPs were extracted from each of the typical channels recorded in sleep studies. They were subsequently included in correlation networks, representing different SAHS-severity degrees, along with the General Conceptual Ability (GCA) score. This cognitive indicator is derived from the battery of tests included in the Differential Ability Scales (DAS), and is commensurate with the intelligent quotient (IQ) [2]. Our main objective was to show the evolution of the EEG spectral content as paediatric SAHS worsens, as well as its relationship with the general cognitive ability of children.

2 Materials

Two hundred and ninety four community non-referral children (5–9 years) underwent an overnight polysomnography (PSG) that included 8-channel EEG (F3, F4, T3, T4, C3, C4, O1, and O2, from the international 10–20 system). Apnoea-hypopnoea index (AHI) was derived from PSG by clinicians according to the rules of the American Academy of Sleep Medicine (AASM) [13]. AHI was used to establish both the presence and severity of SAHS: no-SAHS, AHI < 1 event/hour (176 subjects); mild-SAHS, $1 \leq$ AHI < 5 e/h (98 subjects); moderate-to-severe-SAHS AHI $\geq$ 5 e/h (20 subjects). Table 1 shows clinical and demographic data of the subjects under study. No statistically significant differences (Kruskal-Wallis p-value > 0.05) were found among groups in body mass index (BMI) or age.

EEG was recorded at sampling rates of 250 Hz and 500 Hz that were subsequently homogenized to 200 Hz, as recommended by the AASM [14]. A four-step preprocessing stage was also conducted prior to the analysis of the EEG: (i) re-referencing to the average of all EEG channels; (ii) stop-band filter to 60 Hz and band-pass filter (Hamming window) from 0.1 to 70 Hz; (iii) automatic artifact rejection on the basis of epoch-adaptive thresholding; and (iv) rejection of first and last parts of the EEG to avoid initial and final awake periods.

Table 1. Demographic and clinical data in each SAHS severity group (mean ± Sd)

	no-SAHS	mild-SAHS	moderate-to-severe-SAHS
# subjects	176	98	20
Age (years)	6.60 ± 0.75	6.56 ± 0.75	6.6 ± 0.82
Sex (M/F)	104/72	55/43	10/10
BMI (kg/m^2)	17.10 ± 2.97	18.46 ± 4.82	19.48 ± 5.27
AHI (e/h)	0.39 ± 0.28	1.81 ± 0.83	13.61 ± 10.92

*BMI: body mass index; AHI: apnoea-hypopnoea index; M/F: male/female

DAS tests were administered in the morning immediately after the PSG night [2]. It was composed of a battery of neurocognitive tests that measured the ability among a wide range of intellectual activities [2]. Scores derived from each test were computed in accordance with the age of each child and merged into a single standard score that estimates the global intellectual development (GCA score) [2].

3 Methods

3.1 Spectral Analysis

The power spectral density (PSD) of all EEG channels from all subjects were estimated following the Blackman-Tukey method. Thus, a rectangular non-overlapping 6000-sample window was used to split each EEG channel. The PSDs of the epochs were averaged to estimate a single PSD for each channel of each subject. Then, each averaged PSD was normalized by the total power of the corresponding channel.

The RPs of the conventional EEG frequency bands (*Delta*$_1$: 0.1–2 Hz, *Delta*$_2$: 2–4 Hz; *Theta*: 4–8 Hz, *Alpha*: 8–13 Hz; *Beta*$_1$: 13–19 Hz, *Beta*$_2$: 19–30 Hz; *Gamma*: 30–70 Hz) were obtained from all channels of each subject. RP was computed as the sum of the amplitude values of the normalized PSDs within each frequency band. RPs from six SAHS frequency bands of interests found during the current study were also obtained (Fig. 1). They were found by comparing the grand averaged PSDs amplitude values at each frequency of the different SAHS severity groups using *p*-values from analysis of covariance (ANCOVA) [15].

3.2 Correlation Network Analysis

Weighted correlation network is based on pairwise correlations between variables [16]. In this study, a multi frequency network approach was used in which the RP for each frequency band and channel considered was depicted with a single node in the network. The weighted link between each pair of nodes represents the association between such pair of variables (in terms of monotonic relationship). GCA DAS score was also included as a different node (variable) with the ultimate goal of assessing the interaction between cognitive performance and RPs from EEG.

In order to remove possible bias due to the unbalanced number of subjects in each group, the following split was conducted: (i) 8 subgroups of 22 subjects from the no-SAHS group, (ii) 4 subgroups of 20 subjects and an additional subgroup of 18 subjects from the mild-SAHS group, and (iii) a single group of 20 subjects from the severe-SAHS group. All correlation matrices from a same SAHS-severity group were averaged. Thus, a single matrix was obtained per SAHS-severity group. A non-paranormal transformation was performed for this purpose [17]. Correlation networks were constructed by means of the R package qgraph [18]. Particularly, we used the iterative algorithm described by Fruchterman and Reingold [19], which forces embedded network layouts after 500 iterations.

The whole correlation network analysis was conducted in two cases: (i) using the conventional EEG frequency bands and (ii) the BOIs derived from the statistical analysis of the comparison between groups. Therefore, six networks were obtained (2 cases $\times$ 3 SAHS-severity groups).

3.3 Statistical Analysis

ANCOVA was used to evaluate statistically significant differences when establishing the spectral BOIs (p-value < 0.05). These were corrected for multiple comparisons using the false discovery rate (FDR) methodology. They were also adjusted for age and sex. Spearman's partial-correlation coefficient was used in the correlation networks to assess possible relationships among the RPs of the frequency bands of each channel.

4 Results

4.1 Definition of the SAHS Frequency Bands of Interest

Figure 1 shows the normalized grand average of the PSD (PSDn) from all channels split into the three SAHS severity groups. It also displays the significant p-values (<0.05) reached in the comparison of the PSDn amplitude values from these groups at each frequency. Six BOIs in total were found. The spectral content was mainly concentrated below 5 Hz, where more visual differences arose and up to four BOIs were defined (BOI 1: 0.15–0.38 Hz; BOI 2: 1.17–1.50 Hz; BOI 3: 1.87–2.90 Hz; BOI 4: 3.72–4.63 Hz). All of them were within *Delta 1*, *Delta 2*, and *Theta* bands. However, another two BOIs were present above 39 Hz, within the conventional *Gamma* band (BOI 5: 39.21–58.26 Hz; BOI 6: 61.73–70.0 Hz) with the gap between them coinciding with the values obtained after the 60 Hz stop-band filter.

4.2 Correlation Networks

Figures 2(A)–(F) show correlation networks for the three SAHS severity groups, where the nodes are the RPs of each band and each channel taken as variables. There is another node for the DAS GCA score. Different colors represent each frequency band and DAS. Figures 2(A)–(C) show the conventional EEG frequency bands for each of the SAHS groups, whereas Figs. 2(D)–(F) show the corresponding correlation

networks for the BOIs. The wider the lines that connect each node, the higher the absolute Spearman's correlation coefficient. Red and green colors address the sign of the coefficient (negative and positive, respectively). Absolute correlation values below 0.05 are considered residual and are not represented.

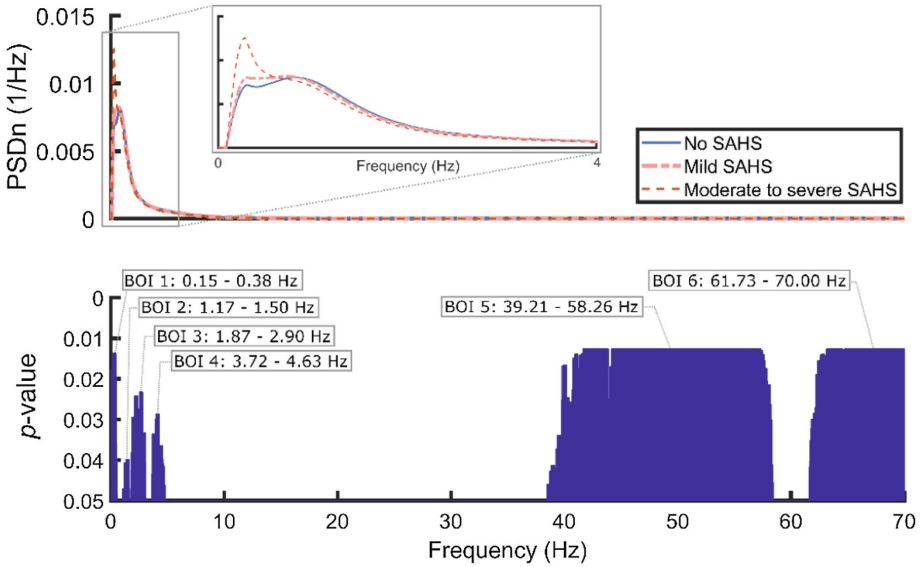

Fig. 1. Normalized grand-average PSD (zoomed in 0–4 Hz) of the three SAHS severity groups and corresponding *p*-values at each frequency. Bands of interests (BOI) 1 to 6 (p-values < 0.05 Kruskall-Wallis test) are also shown.

Correlation networks of the conventional EEG frequency bands show an ordered network for the controls in Fig. 2(A), where the stronger correlations form clusters of channels representing information from the same frequency band.

Clusters gradually disappear as SAHS severity increases in Figs. 2(B) and (C), suggesting higher degree of relationship among the information of the entire EEG spectrum in SAHS presence. Interestingly, the correlation between GCA DAS score and the EEG spectral information also increases with SAHS severity.

Similar tendencies can be observed in the networks formed with the RPs from the BOIs, with the information among the different bands being increasingly correlated as SAHS worsens. Absolute correlations between the GCA DAS score and the RPs from the EEG BOIs also increase with SAHS severity. In addition, the positively correlated clusters formed with BOI 5 and BOI 6 in Figs. 2(D) and (E) may indicate a continuous BOI only disturbed by the 60 Hz stop-band filter.

5 Discussion and Conclusions

In this preliminary study, we have shown differences in the spectral content of the overnight EEG from three different SAHS severity groups: controls (no-SAHS), mild-SAHS, and moderate-to-severe SAHS. We have also presented new spectral BOIs with the potentiality of being more SAHS-specific than the conventional EEG frequency bands. RPs extracted from both these bands and the six BOIs showed lower clustering behavior in the correlation networks as SAHS worsens, indicating that SAHS may be affecting the EEG spectrum in a wide range. This would be consistent with recent studies that reported a continuous impact on the brain due to abnormal breathing during sleep [20]. In both cases, the DAS GCA score increased the absolute value of correlation with the RPs as SAHS severity increased, showing that the cognitive effects in children induced by SAHS could be reflected in the overnight EEG.

BOI 1 (0.15–0.38 Hz) mainly falls within a frequency range in which arousals have particular influence (0.025–0.3 Hz) [21]. As Fig. 1 shows, PSDn amplitudes of SAHS groups are higher than those from no-SAHS are in that region. In addition, it is well-known that arousals often follow apneic events [14]. These circumstances support the specific relationship of this band with SAHS. Moreover, BOI 2 (1.17–1.50 Hz), BOI 3 (1.87–2.90 Hz) and BOI 4 (3.72–4.63 Hz) are mostly included within *Delta* band, whose relationship with non-rapid eye movement (NREM) deeper stage sleep is commonly accepted [22]. Decreasing PSDn values are shown in mild-SAHS and

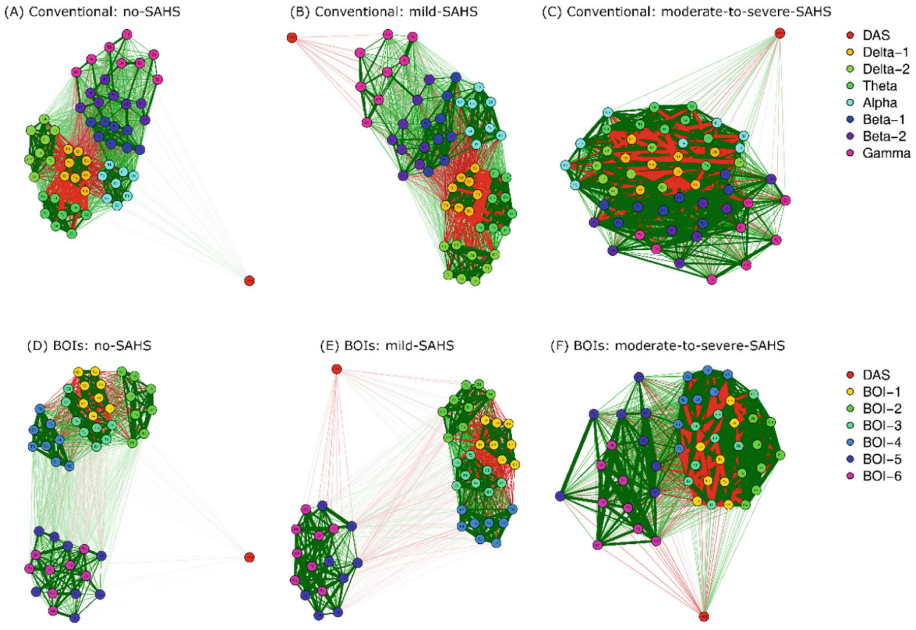

Fig. 2. Correlation networks in the three SAHS severity groups (no-SAHS, mild-SAHS, and moderate-to-severe-SAHS) for the conventional EEG frequency bands (A)–(C) and the new six BOIs found (D)–(F). DAS GCA score is also included in the analysis as a red node.

moderate-to-severe-SAHS groups in these bands, suggesting less deep NREM sleep activity as SAHS worsens. This agrees with the typical sleep fragmentation present in SAHS-affected children [2]. Finally, BOI 5 and BOI 6 are fully included within *Gamma*. This band is associated with active cognitive processing regardless from whether it is generated after external stimuli or internal sources [23]. It has been hypothesized that an association exists between *Gamma* and conscious states [25]. Thus, changes among SAHS groups might be indicating different consciousness degree, which may be due to alterations in the arousal pattern. However, assessment of these hypotheses requires further study.

The cognitive impairment suffered by SAHS-affected children has been well-established [2–5]. However, little research is available regarding possible characteristics in the EEG as reflecting diminished cognitive performance. Weichard et al. [6], reported *Delta* power at the beginning of the night as the key factor underlying specific cognitive and behavioral problems in a cohort of 42 children, a finding which is consistent with the results of the current study (BOIs 2 to 4). On the other hand, Brockman et al. [7], analyzed spindle patterns in both control and SAHS children (33 subjects in total). They found significant correlations between N2-REM stage spindle density from the SAHS group and several neurocognitive tests. These results are also consistent with ours since spindle recurrence and duration are reflected in the band 0.025–0.3 Hz [23], in which BOI 1 is included. These studies, however, focused on single EEG events or frequency bands (*Delta* activity and spindles), whereas our work used a large database to analyze the overnight EEG in an unbiased fashion. This approach allowed us to identify increased absolute correlations of the GCA DAS cognitive score in the entire nocturnal EEG information as SAHS worsens.

Despite the promising results identified in this study, several limitations deserve mention. The proportion of moderate-to-severe subjects should be increased. Although our database is larger than any other used in other state-of-the-art studies, such expansion of the database would be useful for the sake of the generalization of our results. Additionally, subjects from a SAHS clinical referral population would be helpful to validate and enrich our conclusions, as our subjects were selected from the general community. This issue is being currently addressing for future studies. Another future goal is the analysis of our results in accordance with each sleep stage.

To summarize, we have shown that changes in the overnight EEG spectrum arise in the presence of paediatric SAHS. These changes alter both low (BOIs 1 to 4) and high (BOIs 5 and 6) frequencies. The information from the EEG spectrum shows more relationships among all its spectral bands as SAHS worsens. In addition, the spectral information from the EEG has also enhanced relationships with cognitive performance as SAHS severity increases. These results suggest that the spectral information from the overnight EEG, along with its correlation network analysis, can be useful to characterize both paediatric SAHS and identify those children whose cognitive performance is affected by this condition.

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