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# Slow EEG Oscillation to Characterize Pediatric Sleep Apnea and Associated Cognitive Impairments

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*Abstract*— **Previous studies have suggested that the typical slow oscillations (SO) characteristics during sleep could be modified in the presence of pediatric obstructive sleep apnea (OSA). Here, we evaluate whether these modifications are significant and if they may reflect cognitive deficits. We recorded the overnight electroencephalogram (EEG) of 294 pediatric subjects (5-9 years old) using eight channels. Then, we divided the cohort in three OSA severity groups (no OSA, mild, and moderate/severe) to characterize the corresponding SO using the spectral maximum in the slow wave sleep (SWS) band $\delta_1$: 0.1-2 Hz (*Max*$_{SO}$), as well as the frequency where this maximum is located (*FreqMax*$_{SO}$). Spectral entropy (*SpecEn*) from $\delta_1$ was also included in the analyses. A correlation analysis was performed to evaluate associations of these spectral measures with six OSA-related clinical variables and six cognitive scores. Our results indicate that *Max*$_{SO}$ could be used as a moderate/severe OSA biomarker while providing useful information regarding verbal and visuo-spatial impairments, and that *FreqMax*$_{SO}$ emerges as an even more robust indicator of visuospatial function. In addition, we uncovered novel insights regarding the ability of *SpecEn* in $\delta_1$ to characterize OSA-related disruption of sleep homeostasis. Our findings suggest that the information from SO may be useful to automatically characterize moderate/severe pediatric OSA and its cognitive consequences.**

*Clinical Relevance*— **This study contributes towards reaching an objective, quantifiable, and automated assessment of the potential cognitive consequences of pediatric sleep apnea.**

## I. Introduction

Pediatric obstructive sleep apnea (OSA) leads to overnight events of total or partial cessation of respiratory flow in the presence of ongoing respiratory efforts, also termed as apnea and hypopnea events, respectively [1]. OSA is a highly prevalent disease affecting up to 5% of children [2], and the increased risk of cardiovascular dysfunction, cognitive deficits, and behavioral problems are among its most frequent morbid consequences [2]. Particularly, cognitive deficits and decreased academic performance have been frequently reported, with stronger associations being detected as OSA severity increases [2]–[4]. However, there is no viable clinical procedure allowing for routine evaluation of OSA-related cognitive deficits, even though studies have reported reversibility of such deficits if OSA is timely treated [5].

Recent works have focused on analyzing overnight electroencephalography (EEG) to evaluate possible effects of OSA and to detect biomarkers for cognitive dysfunction [6]–[10]. Specifically, alterations in slow wave sleep (SWS) activity, measured as the spectral power in the delta frequency band (δ: 0.1-4 Hz.), has been proposed as reflecting impaired verbal performance and executive functioning [9], [10]. In our latest study on this topic, however, we found that irregularity of low δ ($\delta_1$: 0.1-2 Hz.), measured using the spectral entropy (*SpecEn*), showed stronger relationships with verbal tests (Peabody picture vocabulary test, PPVT3; and expressive vocabulary test, EVT) than δ activity [8]. We suggested that this higher characterization ability of *SpecEn* compared to conventional power (or activity) analysis relied in part on the modifications that we observed in the normal pattern of the slow oscillation (SO) [8]. SO, as the main component of SWS, is typically located around 0.75 Hz and within 0.55–0.95 Hz [11]. We found that this behavior was altered in the presence of pediatric OSA, which gradually showed lower SO frequencies as illness severity increased [8]. We also observed a progressive increase in the SO spectral maximum, leading these concurrent findings to a gradual spectral concentration that explained the *SpecEn* ability to characterize the $\delta_1$ spectrum [8]. Despite these observations, their associations with cognitive and sleep-related variables or with statistical analysis on SO features were not conducted.

In this study, our main goal was to evaluate whether the maximum of SO in the spectrum (*Max*$_{SO}$) and its corresponding frequency (*FreqMax*$_{SO}$) can characterize typical OSA-related variables obtained during the nightm, as well as cognitive deficits in affected children. We also add *SpecEn* in $\delta_1$ to the analyses for direct comparison with already

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published metrics on the topic, and to further elucidate its behavior. We hypothesized that the information contained in these EEG SWS-related features would be associated with both the phenotypic expression of OSA and with negative cognitive effects. Accordingly, we explored these features across three different OSA severity categories (no OSA, mild OSA, and moderate/severe OSA) and evaluated their association with six clinical measures obtained during polysomnography (PSG), the standard overnight diagnostic test, and with six cognitive test results obtained during testing in the morning immediately after PSG.

## II. Materials

### A. Subjects and signals

This study involved 294 nonreferral children (5-9 years old). All the children were recruited after obtaining an informed consent from their parents or legal caregivers. The protocol was approved by the Ethics Committee of the University of Chicago (#09-115-B). OSA diagnosis was conducted through a PSG test while adhering to the technical and clinical recommendations of the American Academy of Sleep Medicine [12], [13]. Accordingly, the apnea-hypopnea index (AHI) was used to establish an OSA diagnosis and its severity. AHI common cutoffs were used to classify the children in three severity subgroups: no OSA (AHI < 1 event/hour, 176 subjects), mild OSA (1 e/h ≤ AHI < 5 e/h, 98 subjects), and moderate/severe OSA (5 e/h ≤ AHI, 20 subjects). Table 1 shows the sociodemographic and clinical characteristics of these children. No significant differences were found among the three subgroups in age ($p$-value > 0.05 Mann-Whitney $U$ test) or sex ($p$-value > 0.05 Fisher exact test). Significant differences were found in standardized body mass index (BMIz) between no OSA and moderate/to severe OSA groups and, as expected, in AHI between all groups.

Eight EEG channels referenced to mastoids were recorded during PSG following the 10-20 international system: F3, F4, C3, C4, O1, O2, T3, and T4, acquired at a sample rate of 200 Hz [12], [14]. A four-step methodology was used as pre-processing stage: *i*) re-referencing to the common average of the 8 channels; *ii*) band-pass filtering between 0.1 and 70 Hz (Hamming window) and stop-band filtering at 60 Hz (both were finite impulse response filters); *iii*) an automatic rejection of artifacts following an epoch-adaptive thresholding approach [8], [15]; and *iv*) rejection of the first and last 15 minutes periods of the EEG to eliminate initial and final awake states.

### B. Cognitive and polysomnographic variables

We used six common PSG-related variables to explore the information obtained from the EEG: AHI, respiratory arousal index (RA, *i.e.* number of arousals per hour of sleep caused by abnormal respiratory events), spontaneous arousals index (SA, *i.e.* number of arousals per hour of sleep whose occurrence is part of the normal sleep physiological process), minimum oxygen saturation value ($Min_{SpO2}$, which is associated to desaturations due to apneic events), sleep efficiency (SleepEff, *i.e.* percentage of minutes spent asleep relative to the total minutes in bed), and sleep pressure score (SPS). This latter variable estimates the degree of sleep disruption in children by computing the proportion of RA relative to all arousals, multiplied by the proportion of all arousals except SA relative to all arousals [16].

TABLE I. Sociodemographic and clincal data (median and interquartile range)

| | no OSA | mild OSA | mod/sev OSA | $p$-value <0.05 |
|---|---|---|---|---|
| **#subjects** | 176 | 98 | 20 | - |
| **Age (y)** | 6.92 (6.50, 7.42) | 6.92 (6.50, 7.42) | 6.81 (6.37, 7.29) | n.s. |
| **Sex (M/F)** | 104/72 | 55/43 | 10/10 | n.s. |
| **BMIz** | 0.65 (-0.11, 1.47) | 0.76 (-0.14, 2.04) | 1.70 (-0.08, 2.24) | [a] |
| **AHI (e/h)** | 0.40 (0.10, 0.60) | 1.50 (1.20, 2.20) | 9.20 (7.30, 17.20) | all |

*BMIz: standardized body mass index; AHI: apnea-hypopnea index; M/F: male/female; n.s.: no significant; a: no OSA vs. moderate/severe OSA comparison*

Six neurocognitive tests were used to evaluate the association between the EEG information and possible OSA-related cognitive impairments: Differential ability scales (DAS), in its composite form, to measure the 'general conceptual ability' [2]; the PPVT3, the EVT, and the NEPSY (for NEuroPSYchological) Phonological Processing (PhPro) to assess the performance in three complementary domains of language, namely receptive, expressive, and phonological processing, respectively; and, finally, the NEPSY Design Copy test (DesCop) to assess visual-spatial processing, and the NEPSY Tower test (Tow) to assess executive functions [2], [8]. All these cognitive scores have already shown decreasing tendencies as pediatric OSA severity increases [8].

## III. Methods

### A. EEG spectral characterization

The Blackman-Tukey technique was used to compute the power spectral density (PSD) of the eight EEG channels from all the children under study. A 6,000-sample length (30 seconds) non-overlapping window was used for this purpose. The PSDs from each channel were normalized (PSDn) by dividing their amplitude values by the corresponding total power. Then, *SpecEn*, $Max_{SO}$, and $FreqMax_{SO}$ were obtained from $\delta_1$ band (0.1-2 Hz). $Max_{SO}$ was simply computed as the maximum value in this band, and $FreqMax_{SO}$ as the frequency at which this maximum is located. *SpecEn* is the application of the normalized Shannon's entropy equation to the PSDn in $\delta_1$. Further PSD normalization was required to assimilate the spectrum in $\delta_1$ to a probability density function, as required by Shannon's equation. Then, it was computed as follows [17]:

$$SpecEn = -\frac{1}{\log N}\sum_{f=0.1\ Hz}^{2\ Hz} PSDn(f)\cdot\log\big(PSDn(f)\big), \qquad (1)$$

where $N$ is the number of frequency bins in the range 0.1-2 Hz. *SpecEn* values closer to 0 represent less spectral components and, consequently, more spectral concentration and regularity in time domain. In contrast, values closer to 1 represent a more equally distributed spectrum among frequencies, *i.e.*, a more irregular signal in time domain [17].

### B. Statistical analysis

As the EEG spectral features did not pass the Lilliefors normality test, the non-parametrical Mann-Whitney $U$ test was used to evaluate statistically significant differences ($p$-value < 0.05) between the three OSA severity groups. Similarly, a

partial correlation analysis was conducted between the spectral features and the PSG-derived variables and cognitive scores. This analysis was conducted per each OSA severity group by adjusting the Spearman's correlation ($\rho$) by age, sex, and wake time after sleep onset (WASO). To compensate for possible bias due to the different size of each group, a bootstrap procedure was used to estimate the correlations. Accordingly, for every OSA severity level, 1,000 bootstrap samples were built with 20 subjects each, which were selected with replacement from the original group. Partial correlations between the EEG spectral features and the PSG and cognitive variables were obtained for each bootstrap sample, and the median of the 1,000 values was considered as the correlation estimation. Only absolute correlations above 0.30 are shown in the results [18].

## IV. Results

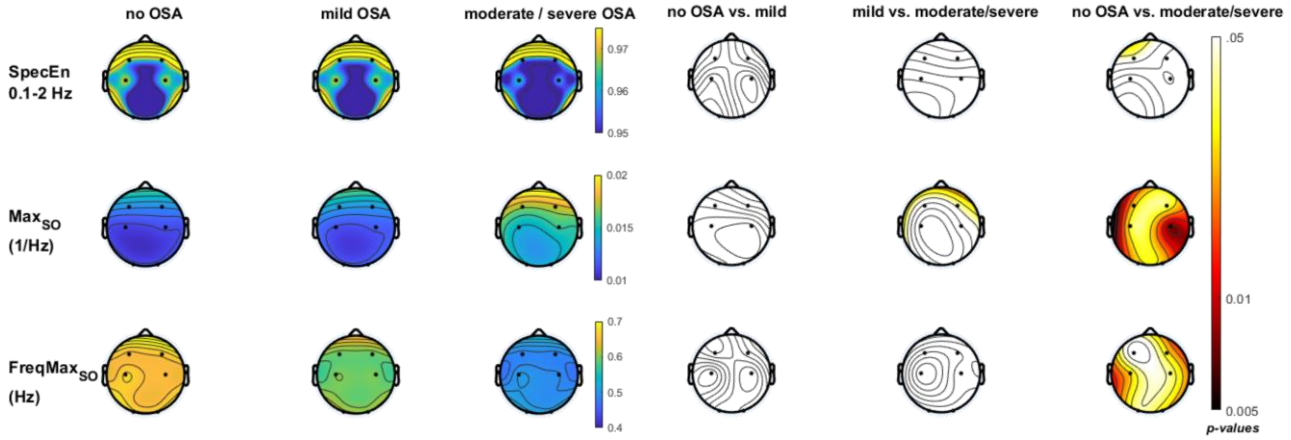
### A. SO differences in OSA severity degrees

Fig. 1a shows the topographical maps of the three EEG spectral features in the three OSA severity groups (mean values). Decreasing tendencies can be observed in *SpecEn* and $FreqMax_{SO}$. Conversely, $Max_{SO}$ increases with OSA severity. Fig. 1b displays the *p*-values in logarithmic scale reached in each channel for each feature in the three possible comparisons: no OSA *vs*. mild OSA, mild *vs*. moderate/severe, and no OSA *vs*. moderate/severe. No differences are observed between no OSA and mild groups in any feature. Moreover, only $Max_{SO}$ shows significant differences when comparing mild with moderate/severe (channels T3, T4, and F4). *SpecEn* only reaches significant differences in F3 when comparing no OSA with moderate/severe, whereas $FreqMax_{SO}$ shows *p*-values below 0.05 in all channels but F3. Finally, $Max_{SO}$ reaches significant differences in all the EEG channels in this same comparison.

### B. Correlation matrix

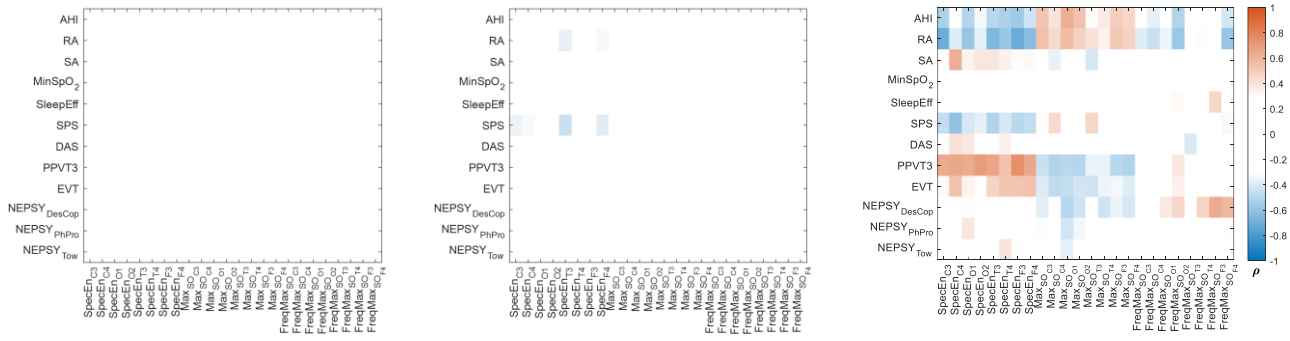
Fig. 2 shows the partial correlations (age, sex, and WASO adjusted) between the spectral features in each EEG channel, the PSG-related variables, and the cognitive scores for each OSA severity group. No absolute correlations above 0.30 were reached in no OSAS (Fig. 2a) and only *SpecEn* in some channels surpassed this threshold for RA and, especially, SPS, in mild OSAS (Fig. 2b). In contrast, the three spectral features reached multiple absolute correlations above 0.30 in moderate/severe OSA. Interestingly, the three of them appear to be associated with RA and AHI in this group. In addition, *SpecEn* also shows relationships with SA and SPS. None of the spectral features showed associations with $Min_{SpO2}$, and only $FreqMax_{SO}$ showed some marginal relationships with SleepEff.

In this moderate/severe group, *SpecEn* and $Max_{SO}$ reached multiple significant associations with the cognitive scores.




a) b)

Figure 1. a) Tendency of the EEG spectral features among the 3 OSA severity degrees and b) pairwise statistically significant differences between them.




a) b) c)

Figure 2. Partial correlation between the EEG spectral features in each channel and the PSG and cognitive variables in a) no OSA, b) mild OSA, and c) moderate/severe OSA. Blue/Red color are negative/positive $\rho$ higher than 0.30 in absolute values. Otherwise, the color is white.

This way, *SpecEn* reached the highest correlations with the DAS test (3 channels in correlations within 0.34/0.41), which is intended for general cognitive assessment. It also showed strong associations with EVT (7 channels within 0.32/0.55) and, especially, PPVT3 (8 channels within 0.54/0.74). Moreover, $Max_{SO}$ also showed robust associations with PPVT3 (8 channels within -0.36/-0.51), EVT (8 channels within -0.33/-0.47), and DesCop (6 channels within -0.36/-0.50). Finally, $FreqMax_{SO}$ also showed significant associations with DesCop (5 channels within 0.38/0.63).

## V. Discussion and Conclusions

In this study, we have expanded on our investigation of the potential associations between the SO information in pediatric OSA and its cognitive consequences. *SpecEn* in $\delta_1$ behaved in a similar way than in our previous work [8], showing meaningful associations in moderate/severe children with respiratory and spontaneous arousals, as well as with PPVT3 and EVT. An interesting novelty is that *SpecEn* also reached significant negative correlations with SPS in both mild and moderate/severe groups, thereby indicating that the lower *SpecEn* (lower irregularity) the higher the sleep homeostasis disruption. This suggests that SWS irregularity may account not only for RA and SA but also for any form of arousal, while highlighting *SpecEn* usefulness as an automatic way to measure disturbed sleep [16].

$Max_{SO}$ and $FreqMax_{SO}$ showed significant differences between no OSA and moderate/severe groups. Additionally, $Max_{SO}$ also reached significant differences when comparing mild and moderate/severe children, thus suggesting that these measures may be particularly useful EEG-based biomarkers for moderate/severe pediatric OSA. This would be supported by the posotive correlations between $Max_{SO}$ and AHI in this cohort. Although the 3 spectral features showed meaningful correlations with AHI, $Max_{SO}$ was the only one whose relationships appear to go beyond those involving arousals, as highlighted by higher correlations with AHI than with RA or SA in several channels. Moreover, $Max_{SO}$ reached negative correlations below -0.30 in all cognitive scores but DAS, with PPVT3, EVT, and DesCop showing these associations in 6 channels or more. This suggests its usefulness to evaluate verbal and visuo-spatial impairments in moderate/severe children. Nonetheless, $FreqMax_{SO}$ seems to be more specific for visuo-spatial processing assessments.

Despite these interesting results, some limitations need to be addressed. First, although the sample size is large, the number of moderate/severe subjects is relatively low compared to the other groups. We have minimized this issue using a bootstrap procedure to obtain the correlation matrices. However, further assessment on moderate/severe subjects would be desirable to generalize our findings. Similarly, the age of the subjects under study is within 5-9 years, which suggests the need for future analyses on other pediatric ranges. In addition, the median AHI of our mild group (1.5 e/h) is very close to the range of AHI values that defines the no OSA group (AHI < 1 e/h), which may be contributing to hide some differences between these groups. Another import feature that deserves comment relates to the fact that these were community children and not a clinical referral cohort, the latter traditionally exhibiting more severe symptoms and OSA.

In summary, we have shown that the maximum of the spectrum in the range 0.1-2 Hz ($\delta_1$) may be used as an OSA biomarker, while also providing useful information regarding verbal and visuo-spatial processing. Similarly, the decrease in the frequency where this maximum is located is specifically related to a decrease in visuo-spatial processing. Finally, we have shown that the EEG irregularity associated to $\delta_1$ could be used as an estimator of sleep fragmentation due to pediatric OSA. Our results suggest that the information from SWS and SO are useful to automatically characterize moderate/severe pediatric OSA and its cognitive consequences.

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