Symbolic dynamics of respiratory cycle related sleep EEG in children with sleep disordered breathing

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***Abstract*— Childhood sleep disordered breathing (SDB) is characterized by an increased work of breathing, restless night sleep and excessive daytime sleepiness and has been associated with cognitive impairment, behavioral disturbances and early cardiovascular changes. Compared to normal controls, children with SDB have elevated arousal thresholds and their sleep EEG may elicit cortical activation associated with arousals but often too subtle to be visually scored. The aim of this study was to assess EEG complexity throughout the respiratory cycle based on symbolic dynamics in children with SDB (n=40) and matched healthy controls. EEG amplitude values were symbolized based on the quartiles of their distribution and words of length 3 were formed and classed into 4 types based on their patterns.**

Children with SDB showed less complex EEG dynamics in non-REM sleep that was unrelated to the respiratory phase. In REM sleep normal children showed a respiratory phase-related reduction in EEG variability during the expiratory phase compared to inspiration, which was not apparent in children with SDB. In conclusion, respiratory cycle related EEG dynamics are altered in children with SDB during REM sleep and indicate changes in cortical activity.

I. Introduction

Childhood sleep disordered breathing (SDB) is characterized by an increased work of breathing, restless night sleep and excessive daytime sleepiness and has been associated with cognitive impairment, behavioral disturbances and early cardiovascular changes that may predispose to an increased risk of developing cardiovascular diseases [1,2,3]. Compared to normal controls, children with SDB have elevated arousal thresholds, and impaired upper airway responses to respiratory stimuli [4, 5]. Importantly, obstructive events in children with SDB are not always terminated with cortical arousal as indicated by high frequency changes in EEG [6]. Cortical activation in children may occur, but be too subtle to visually score. Thus, obtaining markers that reflect brain activation associated with sleep related respiratory loads is still a challenge in clinical practice. Alternative approaches to evaluate neural function in children with SDB that do not rely on standard polysomnography (PSG) EEG criteria include respiratory related evoked potentials [7] and autonomic responses to arousals [8, 9]. Chervin *et al*. proposed to measure subtle changes in cortical activity that occurs phase-locked with respiration, termed respiratory cycle related EEG changes (RCREC). In their initial study, notable differences in average EEG spectral powers linked to the phases of the respiratory cycle were observed in a child with SDB and these differences were reported to diminish after adenotonsillectomy [10]. We recently confirmed the presence of RCREC during sleep in normal children and children with SDB, demonstrating a characteristic reduction in EEG power during the inspiratory phase compared to the respiratory phase [11]. Importantly, the magnitude of RCREC was increased in children with SDB during rapid-eye-movement (REM) sleep and normalized after adenotonsillectomy. Chervin *et al*. speculated that RCREC may represent numerous micro-arousals in response to laboured breathing that is well known to occur in children with SDB, who hypoventilate for most of the sleep periods outside of traditionally scored periods of apnea/hypopnea and arousals. However, the evidence was solely based on correlation analyses and mechanisms have not been elucidated.

The aim of this study was to expand on previous findings on phase-locking between EEG fluctuations and respiratory cycle. We hypothesized that complexity analysis of respiratory cycle related EEG using non-linear methods may reveal further links between breathing and cortical activity. Methods describing non-linear variability such as Correlation dimension, Lyapunov exponents, Kolmogorov-Sinai entropy etc are limited by length of time series analysed. We adopted a novel approach for characterizing and recognizing temporal patterns based on symbolic dynamics that transforms a given time series into short frequency deterministic patterns, usually 3 words long, and evaluates their rate of occurrence, thus quantifying the variability.

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II. METHODS

A. Patients

This study was approved by the Women's and Children's Health Network Human Research Ethics Committee, South Australia, with parental consent and child assent obtained from all participants. Participants were 40 children aged 3.25-12.9 years, with a history of frequent snoring, awaiting adenotonsillectomy for suspected SDB and a matched group of 40 non-snoring healthy controls. More details of the study protocol are published elsewhere [12, 13]. Both groups underwent overnight PSG to evaluate sleep and breathing parameters. It was ensured that participants had not undergone previous ear, nose, throat or craniofacial surgery, or had a medical condition (other than SDB) associated with hypoxia or sleep fragmentation or were taking medication known to affect sleep or cardio-respiratory physiology.

B. Overnight polysomnography

The S-Series Sleepwatch System (Compumedics, Australia) was used to continuously record standard PSG parameters including the electroencephalogram (EEG; C3-A2 and C4-A1) and respiratory movements of the chest and abdominal wall using uncalibrated respiratory inductive plethysmography (RIP). Each child was monitored continuously overnight via infrared camera and by a paediatric sleep technician who also documented observations of sleep behavior. Sleep stages were scored visually in 30s epochs according to the standardized EEG, EOG and EMG criteria of Rechtschaffen and Kales [14].

C. Data analysis

Respiratory data from the thoracic RIP channel, digitized at 25 Hz and EEG data from C3-A2/C4-A1, digitized at 250 Hz, were extracted from the PSG using the programming library libRASCH and analyzed, using custom written algorithms developed with the signal processing toolbox in MATLAB®. The respiratory signal was low-pass filtered at 1 Hz, using a Butterworth forward and reverse digital filter. The resultant respiratory signal had zero phase distortion. In the current study, stage 2 and stage 4 non-rapid-eye-movement (NREM) sleep and rapid eye movement (REM) sleep were considered. Stage 1 and stage 3 NREM sleep were excluded due to their transitional nature and potentially lacking distinction from stage 2. All 30s epochs distorted by respiratory events or movement artifacts as scored by the sleep technicians were excluded from further analysis.

From each retained 30s epoch, expiratory and inspiratory onsets were determined from the thoracic signal by identifying the peaks and valleys using the first-order derivative. These time points were used to extract respiratory cycles and each cycle was divided into six segments: early/mid/late inspiration (*Ins*1, *Ins*2, and *Ins*3) and expiration (*Exp*1, *Exp*2, and *Exp*3), respectively, based on expiratory and inspiratory onsets located on the thoracic excursion signal. The three segments of inspiration and expiration, respectively, were of equal duration.

For each respiratory cycle, corresponding EEG signals (C3-A2) were extracted and transformed into a sequence of symbols [0, 1, 2, 3] as described by Porta *et al.* [15]. The transformation rule was based on the quartiles of their amplitude distribution. Symbol '0' was obtained if the EEG amplitude at a given sample fell in the 3rd quartile of its distribution, '1' if the amplitude was above the 3rd quartile, '2' if the amplitude fell in the 2nd quartile and '3' if it fell in 1st quartile. From the resulting sequence, symbols from within each respiratory segment were extracted and patterns of length $m = 3$ were constructed. Each frequency deterministic pattern was grouped into one of 4 categories:

- all 3 symbols were equal (0V – zero variation),
- two consecutive symbols were equal and the remaining symbol was different (1V – one variation),
- three symbols formed an ascending or descending ramp (2LV – two likewise variations),
- second symbol was larger or smaller than the other two forming either a peak or a valley (2UV – two unlike variations).

Their occurrence expressed as percentage within each respiratory segment (%0V, %1V, %2LV and %2UV respectively).

E. Statistical analysis

Data were analyzed using the statistical software Prism(R) (Graph Pad Inc., USA) version 5.01 for Windows(R) (Microsoft, USA). Normality of data distribution was tested and confirmed using the Kolmogrov-Smirnov tests. To test for group effects, we used two-way ANOVA. One-way ANOVA with post-hoc multiple comparisons using Tukey's method was used to test for within group sleep stage specific respiratory cycle related changes in the parameters. Subject demographic, sleep and respiratory parameters and the symbolic dynamic variables are presented as mean ± SD unless stated otherwise and $p < 0.05$ was considered statistically significant.

III. RESULTS

A. PSG results

Results of overnight PSG have been reported earlier [8, 12, 13, 16]. Briefly, baseline PSG confirmed the presence of

TABLE I. SUBJECT DEMOGRAPHICS, SLEEP AND RESPIRATORY PARAMETERS

	Control (n = 40)	**SDB (n = 40)**
Age (years)	7.5 ± 2.6	7.5 ± 2.7
# males	20	24
BMI percentile (%)	61 ± 26	66 ± 32
TST (min)	447 ± 37	426 ± 60
Stage 2 (%TST)	44 ± 7	42 ± 6
Stage 4 (%TST)	26 ± 5	28 ± 6
REM (%TST)	21 ± 4	20 ± 6
SAI	9 ± 3	8 ± 2
RAI[1]	0.4 ± 0.4	3.2 ± 4.2*
SpO_2 nadir	93 ± 2	91 ± 6*
OAHI[1]	0.1 ± 0.2	5.0 ± 9.0*

BMI body mass index ; TST total sleep time; REM rapid eye movement; SAI spontaneous arousal index; RAI respiratory arousal index; OAHI obstructive apnea-hypopnea index. Data are presented as mean ± SD. [1]Analysis using transformed values.

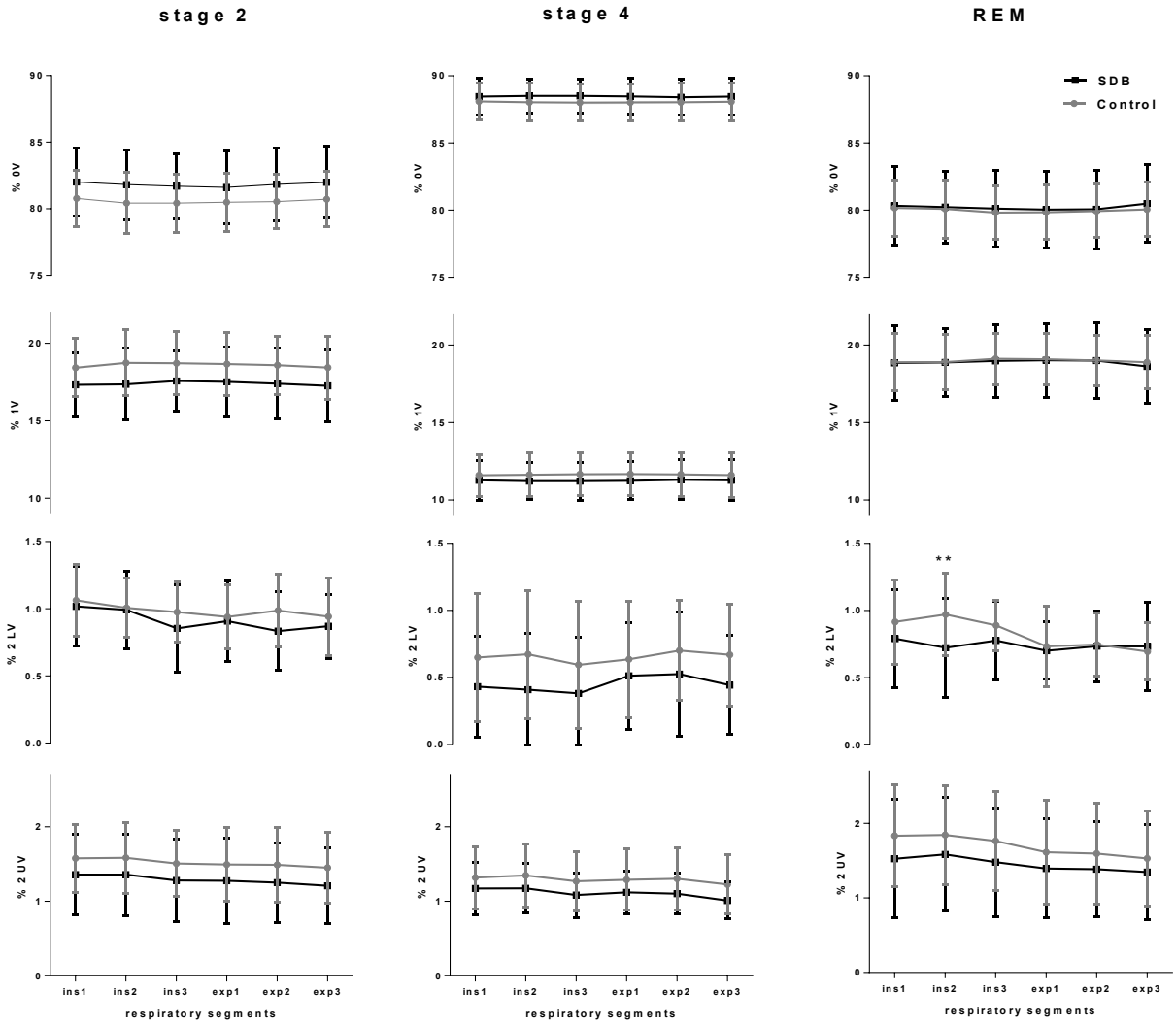

Figure 1: Symbolic dynamics variables %0V, %1V, %2LV and %2UV in normal children (grey) and children with sleep disordered breathing (black) across inspiratory segments (ins1,ins2,ins3) and expiratory segments (exp1, exp2, exp3) of the respiratory cycle. Data are presented as group means and SD. (** p<0.01)

respiratory abnormalities in the children with SDB, who had a significantly higher obstructive apnea-hypopnea index (OAHI), elevated respiratory arousals, increased frequency of SpO_2 desaturations and a significantly lower mean SpO_2 nadir compared to controls (Table I). Overall, the degree of SDB can be considered mild to moderate. There were no significant differences between groups with respect to sleep architecture in the baseline PSG (Table I).

A. EEG complexity phased-locked to respiration

Symbolic word type frequencies as a function of respiratory phase are summarized for normal children and children with SDB in Figure 1. Of the 4 different word types, zero variability word %0V accounted for most of the EEG dynamics, with group average values ranging between 80% and 90%. Comparing sleep stages, %0V words were particularly more common in stage 4 sleep compared to stage 2 and REM sleep. Importantly, in children with SDB, %0V was significantly increased in stage 2 (p < 0.0001) and 4 sleep (p = 0.01), compared to controls. However, no significant respiratory phase effect on %0V was observed in any of the sleep stages.

Low variability, as measured by word type %1V, was observed in 10% and 20% of EEG data on average. Contrasting word type %0V frequencies, %1V occurrence was particularly low in stage 4 sleep, compared to stage 2 and REM sleep. No significant respiratory phase effect on %1V occurrence was observed, but it was significantly reduced in children with SDB during stage 2 (p < 0.0001) and 4 (p = 0.01) sleep.

High variability EEG dynamics patterns were rare and, in case of %2LV, accounted for approximately 0.4% to 1 % of the total dynamics on average. Despite low occurrences, significant group differences were observed, with a reduction in children with SDB across all sleep stages. Post-hoc comparison showed significantly reduced occurrence of

%2LV in the second inspiratory phase segment during REM sleep (Figure 1, indicated by asterisks). A significant respiratory phase effect was observed in both groups during stage 2 (p = 0.002) and in controls during REM sleep (p = 0.001), characterized by a reduction in the expiratory phase. The group and respiratory phase interaction effect was significant during REM sleep (p = 0.04).

High variability EEG patterns of 2 unlike variations (%2UV) occurred slightly more frequently, comprising 1% to 2% of the dynamics on average. Similar to %2LV, occurrences were significantly less frequent in children with SDB than in normal children across all sleep stages. Respiratory phase effect tended toward statistically significance in REM sleep (p = 0.08).

IV. Discussion

In this study we investigated short-term dynamics in EEG throughout the respiratory cycle during sleep in healthy children and children with SDB. In the control group, we observed a significant respiratory cycle-related reduction in EEG dynamics during the expiratory phase compared to inspiratory phase in REM sleep, which was not apparent in children with SDB. EEG dynamics unrelated to respiratory phase were reduced in children with SDB during stages 2 and stage 4 of NREM sleep.

As the applied methodology is only able to capture very fast changes within time frame of 12ms, our analysis is sensitive to high frequency EEG fluctuations. In particular %2LV, which quantifies high frequency EEG dynamics, has shown sensitivity to the respiratory phase as well as significant group differences in SDB children and might therefore be the most relevant of the four symbolic dynamics based parameters. Additional analysis with increased word lengths might capture slow changes sensitive to low frequency EEG fluctuations if any.

Previously we analyzed EEG power changes across the respiratory cycle based on segmenting the respiratory cycle into 4 segments and observed a relative reduction in power during the inspiratory phase across all stages of sleep [11]. Comparing those relative power changes between normal children and children with SDB, significant differences were observed only during REM sleep stage, which tends to increase respiratory instability [11]. Symbolic complexity analysis, on the other hand, suggests that EEG dynamics in SDB children are altered across all stages of sleep.

The physiological basis of respiratory phase-locked EEG fluctuations, in particular during sleep, remains largely unknown. EEG changes linked to respiration have been demonstrated in awake subjects [17] and increased rhythmic fluctuations in intracranial pressure during sleep have been shown to affect EEG [18].

V. Conclusion

Measurement of short-term EEG complexity related to the respiratory cycle during sleep may be useful to quantify changes in cortical activity in children with sleep disordered breathing.

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