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Adenotonsillectomy Improves Slow Wave Activity in Children with Obstructive Sleep Apnea

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Abstract

Objectives: To estimate slow-wave activity (SWA), a marker of sleep homeostasis, in children with obstructive sleep apnea (OSA) before and after adenotonsillectomy (TA) compared with untreated OSA children (comparison group).

Subjects and Measurements: Fourteen consecutively recruited children with OSA (age 6.4±2.5, AHI 10.0±10.3) who underwent TA; Comparison group (n=6) retrospectively recruited children (age 5.4±2.2, AHI 9.4±7.6) with OSA that did not undergo treatment. Electroencephalogram (derivation C3/A2) was analyzed using spectral and waveform analysis to determine SWA energy and slow wave slope. The same procedure was repeated 5.4 and 19 months later for the TA and comparison groups, respectively.

Results: TA improved respiration without a change in duration of sleep stages. Following TA >50% elevation of SWA during the first two sleep cycles ($p < 0.01$), and more physiologic decay of SWA across the night ($p < 0.0001$) were noted. The slope of slow waves increased by >30% following TA ($p < 0.03$). No significant changes were found in SWA in the comparison group.

Conclusions: Sleep homeostasis is considerably impaired in pre-pubescent children with OSA. Adenotonsillectomy restores more physiological sleep homeostasis in children with OSA. SWA analysis may provide a useful addition to standard sleep stage analyses in children with OSA.

Key words: Adenotonsillectomy; Children, OSA, Slow-wave activity

Introduction

Obstructive sleep apnea (OSA) is a common condition with an estimated prevalence of 1–3%. The most common cause of OSA in children is adenotonsillar hypertrophy, thus adenotonsillectomy (TA) is the treatment of choice. Following TA, the majority of children with OSA will have improvement in neurobehavioral function and growth [1–4], and a decrease in health care utilization. [5]

Although pediatric OSA causes substantial neurobehavioral morbidity, at least in part through sleep fragmentation, previous comparison polysomnography (PSG) data have revealed no consistent PSG differences following TA. [1,4,6,7] Some studies demonstrated improvement in sleep efficiency, decreased stage 1 sleep, and increased slow wave sleep (SWS). [2,8,9] Studies exploring distributions of contiguous sleep duration following TA also found no consistent findings. Tal et al. [1] reported no changes in cumulative median duration of sleep stages after TA, while others found some changes, mainly in stage 2. [10] The cumulative data on the effect of TA on sleep stages using traditional PSG scoring are too small to carry the obvious consistent improvement in clinical, neurocognitive, growth, and endocrine changes following TA in children with OSA.

Spectral analysis makes possible the quantitative description of the time course of sleep electroencephalogram (EEG) across the night. Spectral analysis of slow wave activity (SWA) is a quantitative measure of slow-wave sleep dynamics, and represents a physiological marker of homeostatic regulation of sleep. [11] Stronger cortical connections would produce stronger network synchronization and thus a higher level of SWA, whereas weaker connections would reduce network synchronization and

thereby SWA. [12,13] The magnitude of the slope of slow waves can represent an additional measure of SWA. [14] To the best of our knowledge, no studies have been done on SWA in OSA children before and after TA. In adult OSA patients, Heinzer et al. [15] reported a significant increase in mean SWA after continuous positive airway pressure (CPAP) and restored a physiologic decay of SWA across the night.

In the current study we explored SWA in children with OSA before and after TA compared with untreated OSA children (comparison group). We hypothesize that SWA will increase following TA in children with OSA.

Methods

Patients: Included are consecutive otherwise healthy children referred to the Sleep-Wake Disorder Unit for evaluation of possible OSA. Children with other chronic medical illnesses, genetic disorders, facial anomalies, and subjects in two studies with poor quality electroencephalogram (EEG) signals (one from each group) were excluded. Two groups of children were investigated: the treated group (n=14) was consecutively recruited and included children with PSG-proven OSA undergoing TA. The comparison group (n=6) were retrospectively recruited; these were children with PSG-proven OSA who did not undergo surgery or CPAP treatment (Table 1). The institutional ethics committee approved the study protocol.

The diagnostic evaluation included a detailed clinical history obtained using a validated questionnaire in Hebrew [3] that is based on previous questionnaires [2,3,16]. Physical examination was performed by a pediatric pulmonologist and Otolaryngologist.

PSG study: In the laboratory, data were acquired using a computerized commercially available sleep monitoring system (Viasys, SomnoStar Pro, Yorba Linda, CA, USA) as previously described. [1] Parents were guided to maintain their children's normal daily sleep-wake routine and to avoid consumption of soft drinks on the day of the study. Overnight PSG monitoring included recordings of EEG (referential derivations, international 10-20 system, C3/A2, C4/A1, and O2/A1, O1/A2), electrooculogram (right and left outer canthus), electromyogram, and electrocardiogram. Derivation C3/A2 was used for sleep-stage scoring and for power spectral analysis; similar results were obtained using C4/A1. Airflow was recorded using a pressure transducer (Pro Tech Monitoring Inc., Odessa, FL, USA), chest and abdominal efforts were recorded using inductive plethysmography (RespiTrace Plus Viasys, Yorba Linda, CA, USA) and hemoglobin oxygen saturation was monitored by pulse oximetry (Philips Respironics, Pittsburgh, PA, USA). Scoring was done by a trained technician and reviewed by a trained polysomnographer. Sleep/wake and sleep stages were scored according to Rechtschaffen and Kales' criteria. [17] Non-rapid eye movement (NREM) sleep episodes were defined according to standard criteria [18], and adjusted for children [19] because of the frequent occurrence of a "skipped" rapid eye movement (REM) sleep episode after the first NREM sleep episode. Arousals and awakenings were scored using American Sleep Disorders Association (ASDA) criteria [20] with appropriate modifications for children. [1] Obstructive respiratory events during sleep were scored using the traditional criteria. [21] Obstructive apnea was defined as paradoxical breathing for at least two respiratory cycles with complete cessation of nasal airflow. A hypopnea was scored when the paradoxical breathing was accompanied by a reduction of at least 50% in airflow, resulting in either an

arousal or in oxygen desaturation of ≥4%. Apnea Hypopnea Index (AHI) was calculated as the number of respiratory events per hour of sleep.

EEG Spectral and Waveform Analysis: The EEG signals (C3/A2 and C4/A1) were sampled at 100 Hz (12 bit AD converter) and band pass filtered (0.3–35 Hz). Epochs (30-second segments) that contain artifacts such as movement and ocular or muscle artifacts were removed. Respiratory-induced artifacts were removed; these artifacts were minimal when the standard EEG arousal criteria were employed. [1,22] As a consequence, an average of 4.3% and 5.2% of the epochs were excluded from the first and the second night study, respectively. The EEG was analyzed off-line (Matlab R-2008a, The MathWorks, Inc., Natick, MA, USA).

Power spectrum was estimated by Fast Fourier Transform (FFT). Each 30-second epoch was subdivided into 4 second (400 samples) sub-segments (2 second sub-segments yielded similar results) with a 2 second overlap using a hamming window (14 segments each epoch); the power spectral density was averaged, resulting in a 0.25 Hz bin. The absolute energy in each frequency band, expressed in squared microvolts, was calculated for the following bands: delta frequency (often referred to as slow wave activity, SWA, 0.75–4 Hz); theta frequency (4–8 Hz); alpha frequency (8–12 Hz); and beta frequency (12–16 Hz). The total energy of each frequency band was calculated for every 30-second epoch. A smoothed version of the delta energy curve (12-epoch moving average) allows more accurate extraction of the maximum, minimum, and mean of delta energy in every sleep cycle. For standardization of EEG signal analysis, amplitudes were normalized using two approaches: first to total

energy of an artifact-free all-night EEG signal, and second by the mean energy of sleep stage 2 solely.

Waveform analysis was performed according to Rieder et al. [23] The slow wave slope was defined as the amplitude of the most negative peak divided by the time to the next zero crossing of a band-pass filtered (0.75–4 Hz) and smoothed version of the EEG signal. Only waves with consecutive zero crossing separated by one-quarter to one second were considered slow waves. The calculated slow wave slopes were averaged in every 30-second epoch. Both ascending and descending wave slopes revealed similar behavior and therefore only the first was examined.

Data analysis: Statistical analysis was performed using MATLAB. Data were presented as mean±SD unless otherwise specified. PSG data were compared using 2-tailed t-test for paired groups. A linear regression test was performed to determine the correlation between SWA and the slope, and between SWA and AHI or SaO_2. Two-way analysis of variance (ANOVA-2) was used to compare SWA (or slow wave slope) before and after TA or no treatment (factor 1) and sleep duration (factor 2). The null hypothesis was rejected at the 5% level.

Results

Patients: Twenty children participated in this study. Daily routine at home was lights out between 21:00 and 22:00 and mean sleep duration was 9.3 hours (range 8–10) with no significant difference between groups. Mean ages of the TA and comparison groups at the first PSG were 6.4±2.5 years and 5.4±2.3, respectively, and at the second PSG study mean ages were 7.3±2.7 yrs and 7±2.9 yrs, respectively. All

subjects were in the prepuberty age range. The time between the first and second PSG studies was 10.5±7 (range 4–25) and 19±20 (range 6–62) months for the treated and untreated group, respectively ($p = 0.34$). For the treated group, post-PSG studies were repeated 5.4±4 (range 1.5–18) months after the date of surgery. The symptoms reported by the parents for all 20 children prior to the first PSG study are summarized in Table 2. Parents reported mouth breathing during wakefulness, restless sleep, habitual loud snoring, behavioral problems, and upper airway infections. Most parents (12/20 parents) were quite concern about children's symptoms, which motivated them to seek medical help.

Respiratory characteristics: All respiratory parameters improved significantly after TA (Table 1). Mean AHI decreased from 10.0±10.3 to 1.1±1.0 events/hr ($p < 0.002$) after TA surgery. Following TA, 5 of 14 children had REM-AHI equal to NREM-AHI, while the rest exhibited higher REM AHI. Nadir SaO_2 significantly improved after TA surgery (Table 1). In the comparison group a trend toward increased AHI was observed when comparing the first to second PSG results, from 9.4±7.6 to 13.1±7.7 events/hr ($p = 0.07$), respectively.

Sleep architecture: In the TA group there were no significant changes in the cumulative duration spent in any of the sleep stages and in sleep efficiency (Table 1). Arousal + awakening index was significantly decreased following TA (Table 1). Most of the arousals were spontaneously induced and <15% were respiratory-induced. In the non-treated group there were no significant changes in the cumulative duration spent in the sleep stages and sleep efficiency. Arousal + awakening index increased in the second PSG study ($p = 0.04$, Table 1).

EEG Spectral and Waveform Analysis: For both groups, the total energy of sleep stage 2 was 15.1±5.4 mV^2 and 15.1±2.7 μV^2 during the first and second PSG study (p

= 0.6), respectively, without significant differences between the two groups (p = 0.57). Therefore, signals were normalized to whole night total energy and to mean energy of sleep stage 2. Both normalization methods yield similar results; therefore, in this study the presented data correspond to the normalization of sleep stage-2 energy. The normalized power values of the theta, alpha, and beta frequency bands did not change significantly during the night between the first and second PSG studies (treatment factor, F=0.53, $p < 0.47$; F=0.01, $p < 0.93$; F=0.03, $p < 0.87$, respectively, ANOVA 2) – data are not shown. Similar results were obtained for the comparison group. The all-night EEG power spectra for SWS (Stage 3 and Stage 4) and REM (treated group), before and after TA, are illustrated in Figure 1. Normalized EEG power densities during SWS significantly improved following TA in the delta frequency range (0.75–4 Hz, treatment factor, F=39.4, $p < 0.0001$, ANOVA 2), with no significant change in other frequency bands, i.e., theta, alpha, and beta). No significant changes were noted in the power frequency spectrum of REM sleep stage (treatment factor, F=0.79, $p < 0.37$). For the comparison group, no significant changes were noted in power spectra for both SWS and REM (data not shown).

The nocturnal time course of sleep stages (A), absolute SWA (B), smoothed SWA curve (C), and slow wave slope (D) are illustrated in Figure 2 for a single participant pre- (left panel) and post-TA (right panel). No significant change was found in any of the sleep stage durations (Figure 2A and Table 1). However, TA induced considerable elevation of delta energy, i.e., SWA (μV^2; Figure 2B and C), and in the slope of sleep slow waves (μV/sec; Figure 2D). The mean maximal delta energy across the first four sleep cycles in the TA group are summarized in Figure 3A and comparison group in Figure 3B. On first PSG study both groups had a statistically similar SWA pattern (group factor, F=0.19, $p < 0.662$; sleep cycle factor, F=3.73, $p < 0.016$, ANOVA-2).

Following TA, a considerable elevation (>50%) of maximal SWA during the first two sleep cycles was noted (treatment factor, F=6.9, $p < 0.01$, ANOVA-2). Moreover, TA led to more physiologic decay of SWA during the night (Figure 3A; sleep cycle factor, F=20.35, $p < 0.0001$, ANOVA-2). No significant interaction was found between delta energy and sleep cycle (F=1.07, $p = 0.37$, ANOVA-2). No significant changes were noted in normalized SWA energy of the comparison group (Figure 3B; treatment factor F=0.06, $p = 0.8$, ANOVA-2).

A close association was found between SWA and slope: the greater the energy, the steeper the slope for both groups and both PSG studies (for example, see Figure 2C and D). The time course of the slow-wave slope across four sleep cycles is demonstrated in Figure 4. The treated group showed a significant increase in the slope of slow waves following TA across the first three sleep cycles (treatment factor, F=4.7, $p < 0.025$, ANOVA-2), while SWA increased significantly only in the first two cycles (Figure 3).

Discussion

In pre-pubescent children with OSA, TA improved sleep depth, without any significant change in the cumulative proportion of sleep stage duration. Slow wave activity analysis may provide useful additions to the standard sleep stage analyses.

Subjects: We included prospectively recruited otherwise healthy children with typical symptoms for OSA. Removal of the adenotonsillar tissue resulted in improvement of respiration during sleep, but it is possible that children may not have been completely treated by TA, as indicated by abnormal drops of SaO_2 to 93% and REM-related AHI.

Our findings confirm previous reports demonstrating that residual OSA is present in a large proportion of children after TA, mainly in REM sleep [1,7,8]. SWA will not change much if the residual obstructive events following TA occurred during REM sleep, since it is a phenomenon related to NREM sleep. The comparison group retrospectively recruited included otherwise healthy children with OSA who did not adhere to the recommended therapy. In the first PSG study the comparison group was statistically similar to the TA group in OSA severity parameters. The lack of adherence to the recommended therapy was mainly due to the low level of awareness and doubts among parents, physicians, and administrators of the benefits of early TA intervention.

Changes observed in SWA following TA probably reflect a “true” change in sleep depth over treatment. All included subjects in our study were children that at the conclusion of the second PSG study were in their pre-puberty age range; therefore, changes in SWA are unlikely related to puberty. SWA undergoes dramatic changes during brain maturation; it maintains stability across childhood and declines sharply across puberty. [24] A possible limitation of the present study is the “first night effect”, which may affect the sleep architecture of individuals during their first night of the PSG evaluation. However, in a previous study we have shown that the only significant change between two consecutive nocturnal PSG studies was in REM sleep. [25] No change was noted in SWA in the comparison group between the two PSG studies, where each patient served as his own control; thus we do not think the "first night effect" affects our interpretations.

Slow wave activity: EEG signals were normalized to stage-2 energy for standardization between subjects; EEG normalization to the whole night energy yields

similar SWA trends and magnitudes. In the current study normalized SWA improved considerably >50% during the first two sleep cycles following TA compared to the comparison group, supporting the hypothesis that sleep depth is enhanced following surgery. Our findings support the thought that sleep-disordered breathing may prevent physiological homeostatic sleep-drive dissipation, which critically depends on uninterrupted sleep. Others have shown that SWA significantly decreased among adult OSA patients compared to normal controls, when artifact-free EEG signals were analyzed. [26] In the current study, as in previous reports obtained from adults and from children [15,27,28], treatment of sleep-disordered breathing improves slow wave sleep intensity. Thus, all of these studies suggest that sleep-disordered breathing acts upon decreased NREM sleep depth. Why this occurs is unclear. Adult OSA patients may terminate their apneas without clear EEG arousals, but may also stay awake longer. [26] The intensity of SWA correlates positively with the threshold to arouse human subjects or animals. [12] It is possible that in children with OSA, SWA may be forced into reduced sleep depth or other states, such as wakefulness, in order to maintain ventilation during sleep. The initial assumption was that children with OSA do not rouse from their respiratory events during sleep as often as adults do; therefore, sleep architecture is better preserved than in adults. [1,6] Tauman et al. [29] suggested that the decrease in the non-respiratory fraction of arousals represents an effort to preserve sleep homeostasis in children with sleep-disordered breathing. It was suggested that as an effort to preserve sleep homeostasis, children with OSA will develop some form of neural habituation that attenuates the EEG response to upper airway obstruction [22].

It is possible that the improvement in neurocognitive and behavioral function [3,9,30], and growth hormone homeostasis [2,31] following TA in children with sleep-disordered breathing are related to enhancement sleep intensity. A study using a computer model that simulates sleep homeostasis concluded that the decline of SWA could be predicted by a reduction of cortical synaptic strength, which is involved in the generation of slow wave sleep. [14,23] In adult OSA patients it has been demonstrated that the excessive daytime sleepiness may be a result of lack of SWA during the first part of the night. [15] Moreover, experimentally induced sleep fragmentation can reduce SWA [32] and deplete hypothalamic growth hormone releasing hormone that is known to stimulate SWA and growth hormone secretion. [33] In support of this thought, OSA in children can lead to abnormal growth hormone homeostasis that significantly improves following TA. [2,31]

Summary

Children with untreated OSA exhibit decreased SWA level and slope during the night, indicating reduced sleep homeostasis. TA led to more physiological sleep homeostasis in children with OSA. SWA analysis may provide a useful addition to standard sleep stage analyses in children with OSA.

References

1. Tal A, Bar A, Leiberman A, Tarasiuk A.Sleep characteristics following adenotonsillectomy in children with obstructive sleep apnea syndrome. *Chest* 2003; 124: 948-953.

2. Bar A, Tarasiuk A, Segev Y, Phillip M, Tal A. The effect of adenotonsillectomy on serum insulin-like growth factor-I and growth in children with obstructive sleep apnea syndrome. *J Pediatr* 1999; 135: 76-80.

3. Friedman BC, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M, Tarasiuk A, Tal A. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. *Sleep* 2003; 26: 999-1005.

4. Marcus CL, Carroll JL, Koerner CB, Hamer A, Lutz J, Loughlin GM. Determinants of growth in children with the obstructive sleep apnea syndrome. *J Pediatr* 1994; 125: 556-562.

5. Tarasiuk A, Simon T, Tal A, Reuveni H, Adenotonsillectomy in children with obstructive sleep apnea syndrome reduces health care utilization. *Pediatrics* 2004; 113: 351-356.

6. Goh DYT, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. *Am J Resp Crit Care Med* 2000; 162: 682-686.

7. Bhattacharjee R, Kheirandish-Gozal L, Spruyt K, Mitchell RB, Promchiarak J, Simakajornboon N, Kaditis AG, Splaingard D, Splaingard M, Brooks LJ, Marcus CL, Sin S, Arens R, Verhulst SL, Gozal D. Adenotonsillectomy Outcomes in Treatment of OSA in Children: A Multicenter Retrospective Study. *Am J Respir Crit Care Med* 2010 May 6. [Epub ahead of print]

8. Tauman R, Gulliver TE, Krishna J, Montgomery-Downs HE, O'Brien LM, Ivanenko A, Gozal D. Persistence of obstructive sleep apnea syndrome in children after adenotonsillectomy. *J Pediatr* 2006; 149: 803-808.

9. Montgomery-Downs HE, Crabtree VM, Gozal D. Cognition, sleep and respiration in at-risk children treated for obstructive sleep apnoea. *Eur Respir J* 2005; 25: 336-342.

10. Chervin RD, Fetterolf JL, Ruzicka DL, Thelen BJ, Burns JW. Sleep stage dynamics differ between children with and without obstructive sleep apnea. *Sleep* 2009; 32: 1325-1332.

11. Borbely AA. A two-process model of sleep regulation. *Hum Neurobiol* 1982; 1: 195-204.

12. Tononi G. The neuro-biomolecular basis of alertness in sleep disorders. *Sleep Med* 2005; Suppl 1: S8-12.

13. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature* 2004; 430: 78-81.

14. Esser SK, Hill SL, Tononi G. Sleep homeostasis and cortical synchronization: I. Modeling the effects of synaptic strength on sleep slow waves. *Sleep* 2007; 30: 1617-1630.

15. Heinzer R, Gaudreau H, Décary A, Sforza E, Petit D, Morisson F, Montplaisir J. Slow-wave activity in sleep apnea patients before and after continuous positive airway pressure treatment: contribution to daytime sleepiness. *Chest* 2001; 119: 1807-1813.

16. Brouillette RT, Hanson D, David R, Klemka L, Szatkowske A, Frenbach S, Hunt C. A diagnostic approach to suspected obstructive sleep apnea in children. *J Pediatr* 1984; 105: 10-14.

17. Rechtschaffen A, Kales A. A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. US Public Health Service, Washington, DC; 1968.

18. Feinberg I, Floyd TC. Systematic trends across the night in human sleep cycles. *Psychophysiology* 1979; 16: 283-291.

19. Jenni OG, Carskadon MA. Spectral analysis of the sleep electroencephalogram during adolescence. *Sleep* 2004; 27: 774-783.

20. Sleep Disorders Atlas Task Force. EEG arousals: scoring rules and examples. *Sleep* 1992; 15: 173-184.

21. American Thoracic Society: Standards and indications for cardiopulmonary sleep studies in children. The official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 1996; 153: 866-878.

22. Bandla HP, Gozal D. Dynamic changes in EEG spectra during obstructive apnea in children. *Pediatr Pulmonol* 2000; 29: 359-365.

23. Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, Tononi G. I. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. *Sleep* 2007; 30: 1643-1657.

24. Campbell IG, Feinberg I. Longitudinal trajectories of non-rapid eye movement delta and theta EEG as indicators of adolescent brain maturation. *PNAS* 2009; 106: 5177-5180.

25. Reuveni H, Chapnick G, Tal A, Tarasiuk A. Sleep fragmentation in children with Atopic Dermatitis. *Arch Pediatr Adolesc Med* 1999; 153: 249-253.

26. Guilleminault C, Do Kim Y, Chowdhuri S, Horita M, Ohayon M, Kushida C. Sleep and daytime sleepiness in upper airway resistance syndrome

compared to obstructive sleep apnea syndrome. *Eur Respir J* 2001; 17: 838-847.

27. Guilleminault C, Lee JH, Chan A, Lopes M, Huang Y, da Rosa AC. Non-REM-sleep instability in recurrent sleepwalking in pre-pubertal children. *Sleep Med* 2005; 6: 515-521.
28. Guilleminault C, Kirisoglu C, da Rosa AC, Lopes C, Chan A. Sleepwalking, a disorder of NREM sleep instability. *Sleep Med* 2006; 7: 163-170.
29. Tauman R, O'Brien LM, Holbrook CR, Gozal D. Sleep pressure score: a new index of sleep disruption in snoring children. *Sleep* 2004; 27: 274-278.
30. O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner JL, Raffield TJ, Rutherford J, Mehl RC, Wang M, Tuell A, Hume BC, Gozal D. Sleep and neurobehavioral characteristics of 5- to 7-year-old children with parentally reported symptoms of attention deficit/hyperactivity disorder. *Pediatrics* 2003; 111: 554-563.
31. Bonuck KA, Freeman K, Henderson. Growth and growth biomarker changes after adenotonsillectomy: systematic review and meta-analysis. *J Arch Dis Child* 2009; 94: 83-91.
32. Landsness EC, Crupi D, Hulse BK, Peterson MJ, Huber R, Ansari H, Coen M, Cirelli C, Benca RM, Ghilardi MF, Tononi G. Sleep-dependent improvement in visuomotor learning: a causal role for slow waves. *Sleep* 2009; 32: 1273-1284.
33. Obal F Jr, Krueger JM. Biochemical regulation of non-rapid-eye-movement sleep. *Front Biosci* 2003; 8: d520-d550.

Figure Legends

Figure 1: Mean (SEM) all-night electroencephalogram (EEG) normalized power spectral density for NREM SWS (stages 3–4, left panel) and rapid eye movement (REM) sleep (right panel) before (filled circle) and after adenotonsillectomy (TA, empty circle). Power density values (normalized) are plotted every 0.25 Hz bin. For purpose of clarity only the frequency range of 0–10 Hz is shown. Horizontal lines in the top of left panel indicate frequency bins (0.75–4 Hz) in which power density was statistically significant following treatment (treatment factor, F=39.4, $p < 0.0001$).

Figure 2: Example of child sleep analysis, before adenotonsillectomy (TA) (apnea hypopnea index = 27.5 events/hr, left column), and 3.5 months after TA (apnea hypopnea index = 0.3 events/hr, right column) during sleep. (A) Visually scored sleep stages; (B) time course of delta energy, i.e., slow wave activity (0.75–4 Hz, derivation C3/A2); (C) smoothed delta energy (12 epochs moving average); (D) slope of slow waves, i.e., the ratio of the most negative peak and the time to next zero crossing. Slow-wave activity and sleep stages were plotted for 30-second epochs. W – wake; S1 – stage 1; S2 – stage 2; S3+4 – stages 3 and 4, i.e., slow wave sleep; s – second.

Figure 3: Time course of slow-wave activity across four non-rapid eye movement sleep cycles, for adenotonsillectomy (TA) (A) and comparison (B) OSA children. Values represent mean maximal normalized (standard error) slow-wave activity for each non-rapid eye movement sleep cycle. TA significantly improved slow-wave activity (A, open columns) in the first two sleep cycles; indicate by asterisk (treatment factor, F=6.9, $p < 0.01$). No significant changes were noted in the comparison group (B).

Figure 4: Time course of slow-wave slopes in the treated (A) and comparison (B) groups. Values represent the mean normalized slope (standard error) of slow waves for consecutive non-rapid eye movement sleep cycles. On repeated PSG studies (open bars) there was significant improvement (marked with stars) of slow wave slope following TA across first three non-rapid eye movement sleep cycles, indicate by an asterisk (treatment factor, F=4.7, $p < 0.03$); no significant changes were noted in the comparison group. Slope – amplitude/sec.

Table 1: Characteristics of adenotonsillectomy and comparison groups.

	Treated OSA		Non treated OSA	
	1st PSG	2nd PSG	1st PSG	2nd PSG
N	14		6	
Age (years)	6.4±2.5	7.3±2.7	5.4±2.2	7±2.9
Gender (M/F)	7/7		4/2	
Lights off (time)	21:32± 00:33	21:19 ±00:22	21:43±:00:06	21:12±00:25*
TST (min)	424.5±22.7	432.9±34.9	393.5±54.2	448±24.9*
Sleep efficiency (%)	84.3±10.1	83.6±10.5	83.5±7.1	79.2±7.5*
WASO (minutes)	24.8±17.1	31.2±30	27.8±12.1	59.7±26.8*
Ar + Aw index	19.8±10.2	14.0±7.3+	16.0±6.0	21.2±6.6+
S1 (%)	1.7±1.6	1.3±2.1	0.3±0.5	1.5±1.8
S2 (%)	49.9±7.5	48.9±7.1	56.5±9.3	59.2±7.5
S3+4 (%)	30.6±7.4	33.7±6.3	29.3±1.0	26.7±6.3
REM (%)	16.0±7.2	15.0±8.6	13.8±8.8	12.6±7.0
Total AHI (events/hr)	10.0±10.3	1.1±1.0+	9.4±7.6	13.1±7.7
NREM AHI (events/hr)	9.8±11	0.8±1.4	8.8±8.2	15.6±9
REM AHI (events/hr)	15.1±16.7	5.0±10.3	19.3±10	23.5±22.6
Mean wake SaO_2	96.1±1.0	97.5±1.2+	97.6±1.0	96±2.1
Nadir SaO_2	86.1±10.2	92.9±1.7+	90.7±8.1	90.5±3.6

TA group – children with OSA who underwent adenotonsillectomy; AHI – apnea hypopnea index; Ar + Aw index – number of arousal and awakening events per hour of sleep. NREM - Non-rapid eye movement sleep; REM - rapid eye movement sleep; TST – Total sleep time; WASO – wake after sleep onset. Values are mean ± SD; * $p < 0.05$; + $p < 0.02$

Table 2: Symptoms reported by parents prior to PSG study

Symptom	Number of cases
Mouth breathing during wakefulness (≥3 days/week)	10
Restless sleep (yes)	7
Snoring (≥ nights/week)	10
Loud snoring (≥speech loudness)	10
Sweating during sleep (≥2 days/week)	8
Behavioral problems	6
Growth retardation (yes)	5
Respiratory track infections (yes)	7

Presented data are a combination of TA and comparison groups (n=20).

Behavioral problems – parents reporting at least one of the following: shyness, aggression, hyperactivity, and/or discipline problems.

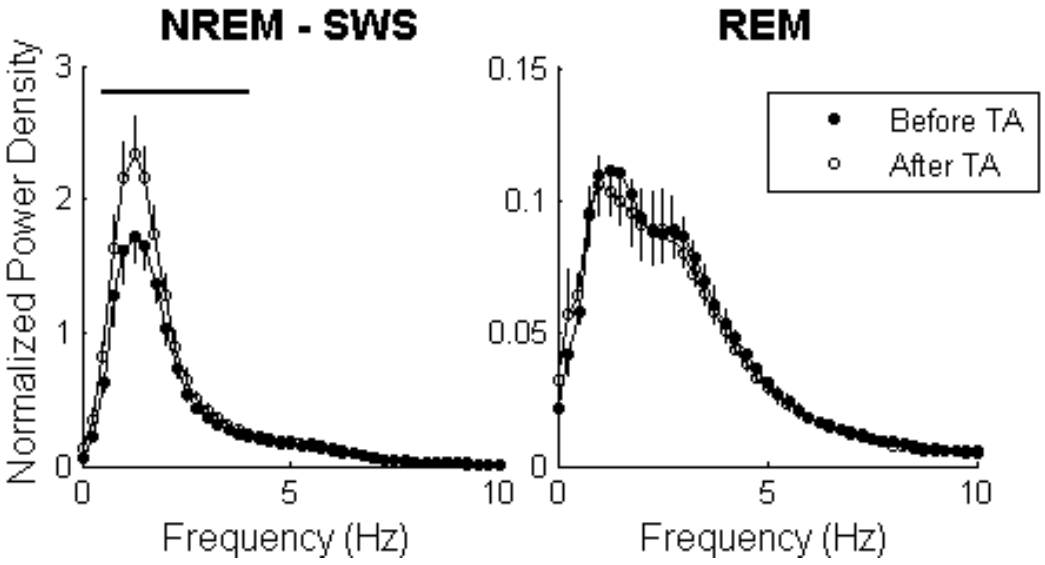
NREM - SWS
REM
Normalized Power Density
Frequency (Hz)
Frequency (Hz)
Before TA
After TA
0
1
2
3
0.05
0.1
0.15
5
10

Figure 1

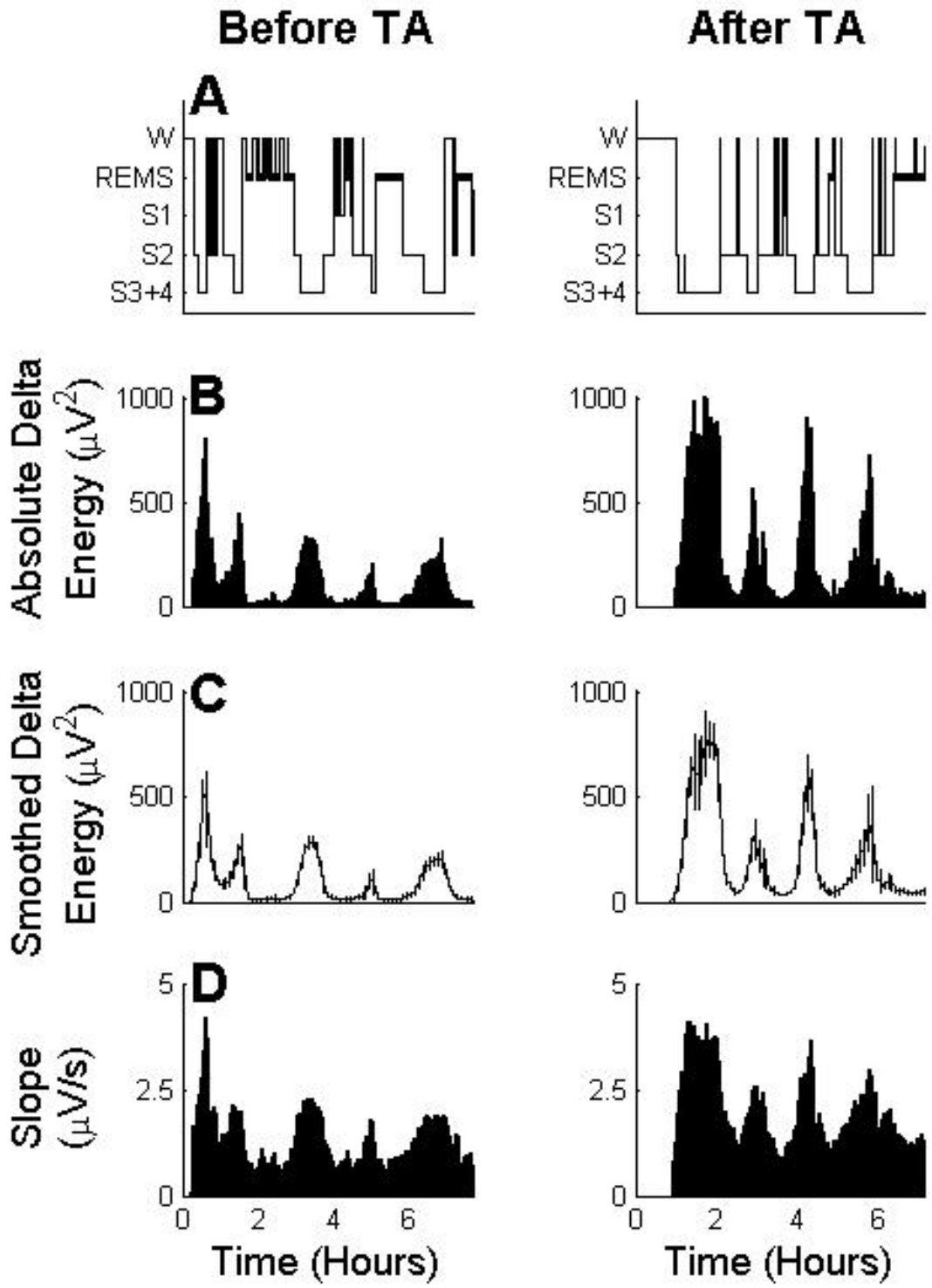
Before TA
After TA
A
W
REMS
S1
S2
S3+4
B
Absolute Delta Energy (μV²)
1000
500
0
C
Smoothed Delta Energy (μV²)
D
Slope (μV/s)
5
2.5
0
2
4
6
Time (Hours)

Figure 2

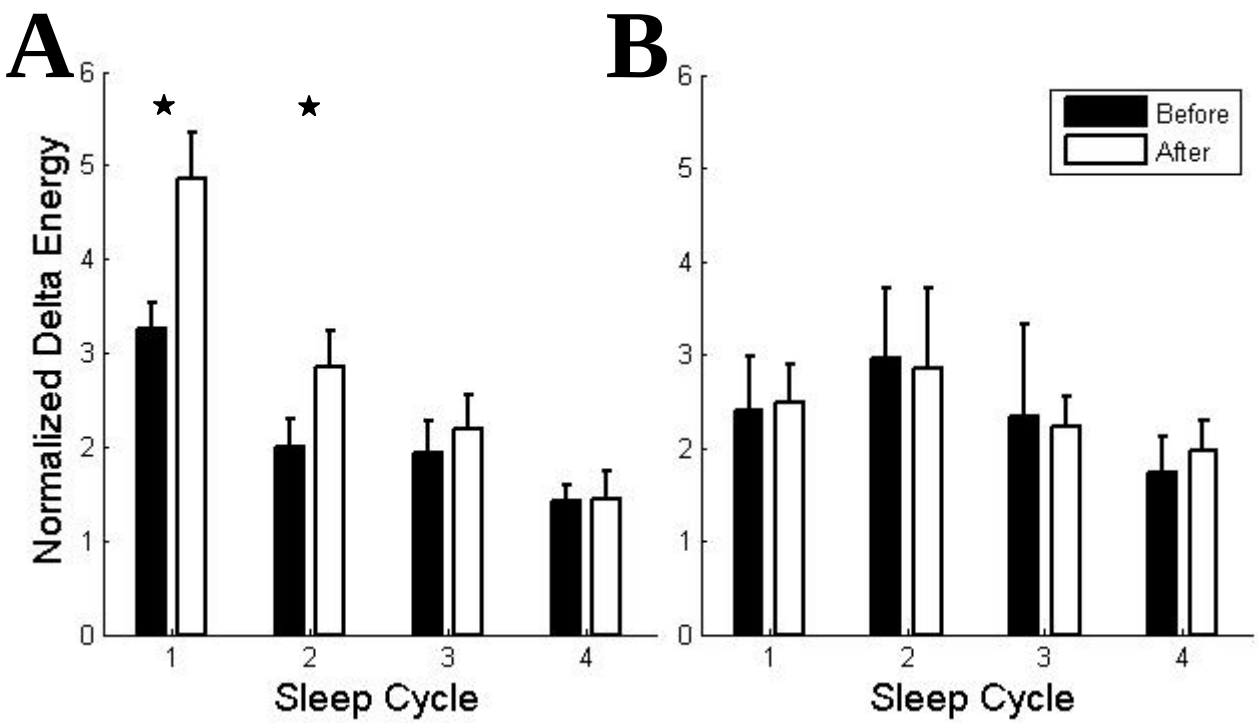
A
B
Normalized Delta Energy
Sleep Cycle
Sleep Cycle
Before
After
0
1
2
3
4
5
6
1
2
3
4

Figure 3

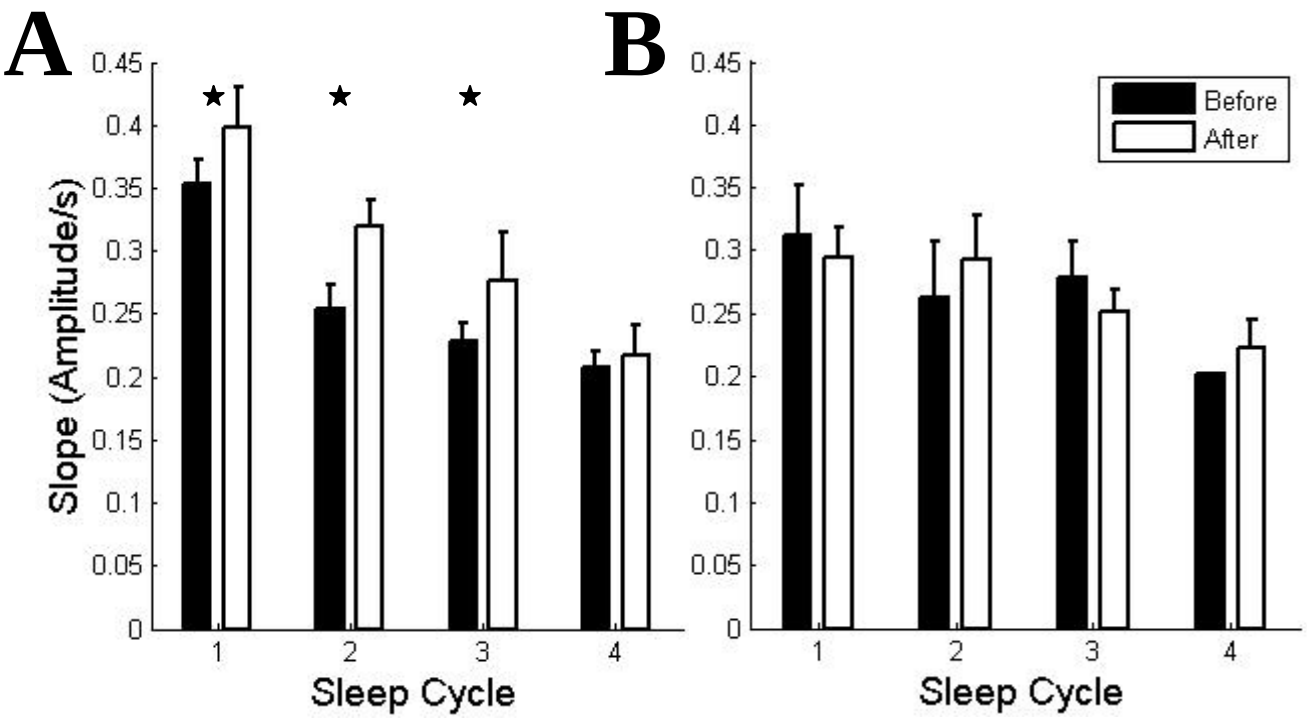
A
B
Slope (Amplitude/s)
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
1
2
3
4
Sleep Cycle
Before
After

Figure 4