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Impairments in Attention in Occasionally Snoring Children: An Event-Related Potential Study

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Abstract

Objective—To determine whether minimal snoring is benign in children.

Procedure—22 rarely snoring children (mean age=6.9 years, 11 females) and age- and sex-matched controls participated in an auditory oddball task wearing 128-electrode nets. Parents completed Conner's Parent Rating Scales-Revised Long (CPRS-R:L).

Results—Snorers scored significantly higher on 4 CPRS-R:L subscales. Stepwise regression indicated that two ERP variables from a region of the ERP that peaked at 844 ms post-stimulus onset predicted CPRS-R:L ADHD Index scores.

Conclusions—Occasional snorers according to parental report do exhibit ADHD-like behaviors. Basic sensory processing is longer than in controls, suggesting that delayed frontal activation requires more effort in snorers.

Over the past decade, the impact of sleep disordered breathing (SDB) in children on cognitive functions has received substantial attention (Arman *et al.*, 2005; O'Brien *et al.*, 2004d; Rosen *et al.*, 2004; M. S. Urschitz *et al.*, 2003). SDB has been repeatedly associated with multiple behavioral and neurocognitive dysfunctions, including restlessness, aggression, excessive daytime sleepiness, and poor school performance (Adams, 2001; N. P. Ali, D; Stradling, JR, 1996; Beebe & Gozal, 2002; Gottlieb *et al.*, 2003; D Gozal, 1998; D Gozal *et al.*, 2001b; D Gozal & Pope, 2001; Hill, 1889; Leach *et al.*, 1992; Rhodes *et al.*, 1995; Singer, 1990; Weissbluth, 1983). In addition, an association between SDB and

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attention-deficit-hyperactivity disorder (ADHD) in children has been documented by multiple investigators (Ball *et al.*, 1997; Corkum *et al.*, 2001; Kaplan *et al.*, 1987; Owens *et al.*, 2000; Ring *et al.*, 1998; Stein, 1999). The need for early diagnosis and treatment of pediatric SDB is further highlighted by the recognition that the age at which SDB is most prevalent (1–8 years) coincides with an important period for neuropsychological development in both humans and animals (Beebe & Gozal, 2002; D Gozal *et al.*, 2001a; E. Gozal *et al.*, 2001c). As further testament of the adverse long-term effects of SDB, Gozal and Pope reported that children who snored during early childhood were at greater risk for poor academic performance in later years, long after snoring had resolved (D Gozal & Pope, 2001). This unique vulnerability to insult by SDB in the rapidly developing brain could be a key difference in adult and pediatric forms of the disease (Halbower & Mahone, 2006; E. Gozal *et al.*, 2001c).

In 2002, the American Academy of Pediatrics (AAP) recommended that all children who habitually snore should be evaluated (American Academy of Pediatrics, 2002), while earlier literature suggested that the presence of snoring was important only insofar as it served as a potential, albeit unreliable, marker for more severe forms of SDB such as obstructive sleep apnea (OSA) (N. Ali *et al.*, 1993; Gislason & Benediktsdottir, 1995; D Gozal & Pope, 2001; Guilleminault *et al.*, 1976; Guilleminault *et al.*, 1982). Based on recent studies reporting neurocognitive dysfunction and impaired daytime performance in children who snore in the absence of overt or clinically diagnosed OSA (Alexopoulos *et al.*, 2006; Guilleminault & Lee, 2004; Lopes & Guilleminault, 2006; O'Brien *et al.*, 2004a; O'Brien *et al.*, 2004b), some authors proposed that parental report of snoring may operate as one of the most robust predictors of cognition and school performance (Beebe, 2006). Habitually snoring children are at higher risk for impaired academic performance, increased social problems, decreased attention, impaired visuospatial ability, and poorer scores on measures of anxiety and depression (Blunden *et al.*, 2005; Chervin *et al.*, 2005; O'Brien et al., 2004a; M. Urschitz *et al.*, 2004; M. S. Urschitz et al., 2003). Consequently, habitual snoring may soon become considered as the mildest form of SDB, rather than be dismissed as clinically irrelevant (Guilleminault & Lee, 2004). The case for occasional snoring in non-habitual snorers having no adverse consequence has been largely ignored in the literature under the assumption that occasional snoring should be viewed as a truly benign condition, (Kuehni *et al.*, 2008; M. Urschitz et al., 2004). Unfortunately, occasional snorers have not been considered a distinct group, and their inclusion in studies investigating SDB in children has been rather inconsistent. Most often, these non-habitual snorers are combined with non-snorers in the control group of children who do not have SDB (Karpinski *et al.*, 2008; Liukkonen *et al.*, 2008; O'Brien et al., 2004a; M. S. Urschitz et al., 2003). It is possible that these methodological inconsistencies and the underlying assumption that occasional snoring imposes no adverse consequences may account for the high degree of variability across reports concerning the neurobehavioral sequelae associated with SDB in children.

To examine whether a putatively benign condition such as occasional snoring is associated with altered brain function, we applied a highly sensitive approach, namely event-related potentials (ERPs). This method—and the attention paradigm described below--has been used in adults with SDB to investigate patterns of brain activation underlying behaviorally observed deficits in domains such as attention (Gosselin *et al.*, 2006a; Gosselin *et al.*, 2006b). The recording of ERPs is a highly sensitive technique that is both safe and well tolerated in children and infants. ERPs can detect (and in some cases predict) significant neuropsychological differences even in the absence of gross findings (Lyytinen *et al.*, 2001; Lyytinen *et al.*, 1992; Lyytinen & Naatanen, 1987; Molfese & Molfese, 1985; Molfese, 1989, 1990, 2000; Molfese *et al.*, 2006).

We hypothesized that occasional snoring may would disrupt neuropsychological functioning with snoring children exhibiting impaired activation over frontal and prefrontal areas, areas normally associated with attention. The experiments described herein examined differences in ERPs recorded during a classic attention task between a group of pre-pubertal community children who snored "rarely" or "occasionally" according to parental report and a matched control group who had no history of snoring. Dependent ERP variables were then analyzed in relation to sleep measures and scores on a standardized and sensitive measure of neurobehavioral functioning in children with SDB, the Conner's Parent Rating Scales-Revised: Long (CPRS-R: L) (Wei *et al.*, 2007). Furthermore, this decrease in cognitive reserve was hypothesized to predict observable neurobehavioral problems as measured by the CPRS-R:L.

METHODS

Participants

Participants included 44 children between 4 and 8 years of age (mean age=6.92 years, SD=1.24, 22 females). Subjects were selected on the basis of parental responses to items on the Sleep Behavior Questionnaire (SBQ, described below) concerning snoring frequency and severity. Children who were reported to snore either "Rarely" or "Occasionally," were assigned to the non-habitual snoring group. Children for whom parents selected "Never" were assigned to the control group. For both groups, the presence or absence of snoring was confirmed during an overnight sleep study (PSG). Children were tested as part a larger, on-going study of sleep characteristics in healthy children. They were financially compensated along with a bag of books, puzzles, and toys for their participation in the larger study. All subjects were recruited and consented according to the guidelines of the American Psychological Association. Approval of the Institutional Review Board of the University of Louisville was obtained prior to the start of the study. A photograph of a participant wearing the 128-electrode net used to record the ERPs is shown in Figure 1.

Exclusion criteria for both groups included: pre-existing medical, neurological, psychiatric, behavioral, or learning disorders indicated by screening questionnaires on history; medication usage; obesity (BMI greater than 95th percentile); significant growth failure; developmental delay; failure to pass the hearing and vision screening (using air conduction threshold tests in the same normal range for both ears as a hearing test and tumbling-E Snellen charts for a measure of approximate visual acuity); failure to pass IQ screening (using the Peabody Picture Vocabulary Test III as a proxy for IQ described below); first-degree relative with a major affective disorder or mental illness assessed by family history diagnostic criteria; and significant "at-risk" scores on the Childhood Symptom Inventory-4 (described below). A licensed psychologist clinically interviewed children (and their parents) whom the CSI-4 determined to be "at risk." Children with significant behavioral disorders were excluded. The final sample included 22 children in the non-habitual snoring group and 22 age- and sex-matched controls. Both groups comprised 11 males and 11 females each. Table 1 outlines pertinent demographic information for this sample. There were no significant group differences for any demographic variable.

Apparatus and Procedure

ERP Apparatus and Procedures—Equipment: A high-density 128 Ag/AgCl electrode system utilizing high-impedance amplifiers (EGI, Eugene, OR) was used to record ERP activity. NetStation © software (EGI, Eugene, OR) controlled impedance measures, baseline correction, analog/digital sampling rate, artifact rejection, and averaging. A second computer used e-prime © software to present stimuli, integrating this information with the ERP recording software. Interstimulus intervals (ISI) varied randomly between all stimuli.

Testing Methods: Children were tested individually in sound-dampened rooms at the Sleep Center the morning following their overnight PSG sleep study. Screening tests were administered, including hearing (air conduction threshold) and vision screening (Snellen charts) and behavioral testing. The child's head was measured, and the vertex was marked for proper alignment of electrode net placement. Following standard procedures, the electrode net was soaked for 5 minutes in warm KCl solution. Net application and impedance adjustments required less than 5 minutes. Electrode impedances, recorded prior to and at the end of each task, were below 40 kOhms to maximize signal-to-noise ratio, thereby produce a high-quality signal for subsequent analyses. ERP signals were digitized on-line at 4 ms intervals for a 1.5 sec period for each of the 128 sites. Filters were set at 0.1 Hz for high pass and 30 Hz for low pass, with a gain of 10K. The system collected auditory and visual ERPs as the child participated in 3 tasks. If the child moved, recording was paused until the child was sitting quietly. Children took 3-minute breaks at the end of each task. ERP testing lasted about 50 minutes.

Electrophysiological Task: The "oddball" or "P300" task is a classic attention task in the ERP field (Sutton et al., 1965). The findings have been consistent across numerous studies over a variety of populations, including studies of sleep apnea. In fact, the P300 peak (also referred to as subtype P3b) is the most widely studied ERP component in adults and children. The results of this task are related to a wide range of behavioral assessments of attention and provide a direct link to the cognitions of attention and vigilance. The amplitude of a positive peak occurring about 300 ms after stimulus onset is larger in response to infrequent events in adults. In healthy children, this peak typically occurs approximately 400 ms (Emmerson *et al.*, 1990; Key, 2005; Polich & Martin, 1992).

Stimuli: Two single frequency tones, 300 ms duration, selected from a range between 1000 and 4000 Hz served as stimuli. Tones presented during any test differed by 500 Hz. Rise and decay times were matched between stimulus pairs. Auditory stimuli had matched loudness levels, 75 dB SPL(A), and were presented through a speaker one meter over the midline of the child's head.

Pre-test Training: Before testing, the child listened to a series of two "beeps" that occurred at 1-second intervals. One tone occurred with high frequency (four times in a row). The second (target) always occurred on the 5th, 10th, 15th, and 20th trials. Children quickly learned to press the correct button to the tone presented in less than 20 trials.

Task: The experimental task presented two tones at 2-second intervals. Tones occurred in random order, so that one occurred on 70% of the trials while the other occurred on 30%. To decrease habituation and learning, tone frequency changed across test sessions for each child, and frequency of occurrence for the higher tone vs. the lower was counterbalanced across sessions, children, and sex. The test presented 120 tones. The tester asked the child to attend to the target and press a button on hearing it. Tone presentation lasted 5 minutes.

PSG Apparatus and Procedures—All children and one of their parents reported to the Sleep Laboratory around 7:30 pm. Following adaptation to the testing environment and personnel, the sleep studies began between 9:00 and 9:30 pm. The following parameters were measured: chest and abdominal wall movement by respiratory impedance or inductance plethysmography, heart rate by electrocardiogram (ECG); air flow with a sidestream end-tidal capnograph (PETCO2; BCI SC-300, Menomonee Falls, WI) which also provided breath-by-breath assessment of end-tidal carbon dioxide levels, nasal pressure and an oral-nasal airflow thermistor. Arterial oxygen saturation (SpO2) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc., Hayward, CA), with simultaneously recorded pulse

waveform. Bilateral electro-oculogram (EOG), 8 channels of electroencephalogram (EEG), chin and anterior tibial electromyograms (EMG), and analog output from a body position sensor (Braebon Medical Corporation, NY) were also monitored. All measures were digitized using a commercially available computerized PSG system (MedCare Diagnostics, Buffalo, NY or Stellate Systems, Montreal, Quebec, Canada). Tracheal sound was monitored with a microphone sensor (Sleepmate, VA) for detection of snoring and digital time-synchronized video images were collected. The sleep technician followed patient behavior and confirmed sleep position by the infrared camera inside the room. The presence of snoring was verified in occasionally snoring children provided that at least 10 min of observed snoring would be present during sleep. Conversely, the absence of snoring was confirmed as well for control children. All the studies were initially scored for both sleep stages and respiratory events by a certified technician and were then reviewed by physicians experienced in pediatric polysomnography (Rechtschaffen & Kales, 1968). The proportion of time spent in each sleep stage was expressed as percentage of total sleep time (%TST). Central, obstructive and mixed apneic events were counted. Obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for duration of at least two breaths (Montgomery-Downs *et al.*, 2006; American Thoracic Society, 1996). Hypopneas were defined as a decrease in oronasal flow of ≥50% with a corresponding decrease in SpO_2 of ≥4% and/or arousal (Montgomery-Downs *et al.*, 2006). The obstructive apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of TST. The mean oxygen saturation, as measured by pulse oximetry (SpO2) in the presence of a pulse waveform signal void of motion artifact, and the nadir SpO2 were recorded. Arousals were expressed as the total number of arousals per hour of sleep time (arousal index), and were defined as recommended by the (American Sleep Disorders Association Task Force, 1992) and included respiratory-related (occurring immediately following an apnea, hypopnea, or snore), technician-induced, and spontaneous arousals.

Behavior Apparatus and Procedures—The Sleep Behavior Questionnaire (SBQ) provided support for the PSG results and was used to initially define conditions as control or snoring on the basis of parental reports. A proxy for IQ was obtained using the Peabody Picture Vocabulary Test-III (PPVT-III) and used as a screener. Participants' socioeconomic status and hand preferences (using the Edinburgh Handedness Inventory, Oldfield 1971) were previously obtained and are not reported here. The Childhood Symptom Inventory-4 (CSI-4) screened for extreme behavioral disorders and characterized the neurocognitive status of children with and without SDB. The NEPSY is a standardized neuropsychological assessment that has been used previously in studies of children with SDB. It was used as a measure of observable neurocognitive function. The Conner's Parent Rating Scales-Revised (CPRS-R:L) is a widely used tool that is sensitive to the behavioral changes associated with SDB and habitual snoring. It was used as a measure of parental perception of neurobehavioral functioning and was the criterion predicted by the ERP variables in the multiple regression analysis described below.

Sleep Behavior Questionnaire: Parents of all Sleep Medicine Center patients completed a detailed questionnaire about sleep problems, habits, and practices. Questions pertained to bedtime routines (e.g., "Will your child fall asleep alone in bed?" "In order to fall asleep does your child need a special toy or object?"), as well as sleep disturbances such as daytime sleepiness, restless sleep, nightmares, sleepwalking, nocturnal enuresis, sleep apnea, snoring, and nocturnal awakenings. The majority of questions were dichotomous with 'yes' or 'no' answers; however, some items were open-ended or multiple-choice responses (e.g., "What do you think that prevents your child from falling asleep?"). In previous studies from the Sleep Medicine Center, the SBQ had a high sensitivity and specificity for snoring and non-snoring children in this age range (Montgomery-Downs *et al.*, 2004). For this study, the

SBQ was used as a measure of parental report of sleep parameters, as the basis for group assignment as snoring or non-snoring, and to obtain background information such as demographics and history of sleep issues for each participant.

Childhood Symptom Inventory 4 (Gadow & Sprafkin, 2002): The CSI-4 Parent Checklist was used to screen for behavioral, emotional, and cognitive disorders based on parent-reported symptoms outlined in the DSM-IV. The tool was developed for use as a diagnostic and screening measure in clinical psychiatric and special education populations. Use of the CSI-4 to identify participants who should be excluded due to psychiatric or behavioral disorders was justified for this study. The questionnaire listed a variety of symptoms and the parent indicated whether the particular symptom "never," "sometimes," "often," or "very often" characterized the child. The parent completed the CSI-4 at the initial overnight sleep study. If a child's score indicated that he or she was at risk, a clinical psychologist evaluated the child. The internal consistency of the CSI-4 was high in general, with Chronbach's alpha values ranging from .94 to .74 for the Parent Checklist categories. Test-retest reliability correlations for the symptom count and symptom severity scores were high (For example, the Pearson Correlation for the AD/HD Hyperactive-Impulsive Type Symptom Severity Score between the initial session and the retest was 0.84) and all were significant at an alpha level of 0.0001 with a testing interval of 4 weeks. In this study, however, the CSI-4 was used only once (see timeline above) as a screening measure.

The CSI-4 was used for children 5 to 8 years of age. Four-year-olds were given the version of the symptom inventory for younger children (Early Childhood Inventory 4, ECI-4). The diagnosis of a behavioral disorder was not determined from the CSI-4. Rather, children identified as "at-risk" due to a high symptom severity score on the CSI-4 (indicating a high occurrence of problem behaviors as identified by the DSM-IV) were referred to a clinical psychologist for a formal interview and assessment. The child was then excluded from the study if a clinical diagnosis was received.

Peabody Picture Vocabulary Test-III (Dunn & Dunn, 1997): The PPVT-III was used as an IQ-screening tool and as a measure for characterizing the sample. The PPVT-III is the most widely used measure of receptive language abilities. It was co-normed with the Expressive Vocabulary Test thereby allowing for direct comparison of expressive and receptive language for individuals aged 2.5 to 90+ years. The assessment was individually administered and untimed, with children selecting the one picture of four choices that best corresponded to the word the tester read. The test has high reliability and internal consistency in young children and adults with reliability coefficients for the raw and standard scores ranging from 0.88 to 0.99 for all age groups (testing interval was one month) and Chronbach's alpha ranging from 0.92 to 0.98. For the purposes of this study, the PPVT-III was administered once. The assessment has high construct validity, with correlations between the PPVT-III standard scores and the Wechsler Intelligence Scale for Children-Third Edition (WISC III) ranging from 0.82 to 0.92 for the norming sample. Vocabulary measures obtained with tests such as the PPVT-III are used as a proxy measure of overall intelligence and are related to language-based outcomes, such as those utilized in the present protocol. The test was administered before PSG and required approximately 15 to 20 minutes for children between 4 and 8 years of age.

NEPSY (Korkman et al., 1998): The NEPSY is a battery with five subtests used to provide an assessment of neuropsychological functioning in children from 3 to 12 years of age. These were measures of basic and complex cognitive capacities that affected learning and school performance. There are five domains: Attention/Executive Function, Language, Sensorimotor, Visuospatial Processing, and Memory and Learning. The NEPSY was administered twice as part of the larger overall study. Initial test scores for the Visual

Attention subtest assessed whether ERP differences in response to an attention task relate to differences in observable behavior during a standardized attention test. During this subtest, children are shown an example of a picture ("bunny," "cat," or "faces") and asked to mark all identical figures in an array in under 3 minutes. Each child is given 2 arrays. The NEPSY has high test/retest reliability (e.g. an adjusted r squared of 0.9 for the Memory and Learning component) across sex and ages (3–12 years) even with a testing interval as short as 2 to 10 weeks. The internal consistency of the NEPSY is also high with r values ranging from 0.71 to 0.91 for all domains across the age range included in this study (4 to 8 years). The administration time for this test was approximately 6 minutes.

Conners' Parent Rating Scales-Revised: Long (Conners, 2000): The CPRS-R: L was originally published in 1970 by C. Keith Conners, PhD. The revised version was released in 1997. It was developed using a normative sample of over 8,000 children in the United States and Canada. It uses parental ratings to assess ADHD and problem behaviors in children aged 3 to 17 years. The CPRS-R: L has been widely used for research and clinical purposes, including screening, diagnosis, treatment planning, and outcome assessment. The questionnaire contains 80 Likert items assessing 7 factors: oppositional, cognitive problems/inattention, hyperactivity, anxious-shy, perfectionism, social problems, and psychosomatic. It provides 14 subscale scores: oppositional, cognitive problems/inattention, hyperactivity, anxious-shy, perfectionism, social problems, psychosomatic, ADHD Index, CGI: restless-impulsive, GCI: emotional lability, CGI: total, DSM-IV: inattentive, DSM-IV: hyperactive-impulsive, DSM-IV: total. The CPRS-R: L has been extensively used in other studies of pediatric SDB (O'Brien *et al.*, 2004c; Wei et al., 2007).

ANALYSES

Analysis of Electrophysiological Data

Initial ERP Data Treatment—Initial ERP data treatment or "preprocessing" was conducted using commercially available NetStation © software, version 4.1.2 (Electrical Geodesics, Inc., Eugene, OR). Single trial ERPs were screened following standard procedures for eye artifacts. Electrodes at standard electro-oculogram (EOG) positions measured eye movements. Trials with eye channel differences in excess of 70 μV or more than 5% bad channels (defined as detecting voltage shifts in excess of 150 μV within and across trials) were rejected. Channels characterized by consistent high voltages were replaced using a spherical interpolation algorithm. Following artifact screening, the EEGs were baseline corrected, using the 100 ms prestimulus average as a measure of baseline. ERPs were adjusted using a 30 Hz digital low pass filter and an average reference. Trials were then averaged for each subject separately (Andreassi, 2000; Regan, 1989).

Principal Components Analysis (PCA) - Repeated Measures Analysis of Variance (RMA)—Analysis of the preprocessed ERP data was conducted using the commercially available software package Statistical Software for the Social Sciences (SPSS) ©, version 11 for Mac OSX (SPSS, Inc., Chicago, IL). Investigators used spatial principal components analysis to identify variation in the distribution of activity across the scalp and determine regions of the topographic distribution that were significantly correlated. These covarying clusters of channels were then averaged to form the seven "virtual electrodes" outlined in Figure 3 in the results section of this paper. This reduced the data to meaningful measures and provided "virtual electrodes" that were subjected to temporal PCA with Varimax rotation to identify distinct regions of temporal variability in the waveform. The PCA-Varimax procedure was blind to individual experimental conditions and generated the same solution regardless of the order in which data were entered. PCA has less variance

misallocation than traditional amplitude-latency measurements—or “peak-picking”--if sufficient power exists (Beauducel & Debener, 2003).

After PCA was used to identify the major ERP components, subsequent factor weights served as the dependent variables in a Repeated Measures Analysis of Variance (RMA) that tested the null hypothesis of $\mu_{SNORE} = \mu_{CONTROL}$ for the electrophysiological task. The mixed-factorial RMA utilized the design, Group (2) × Stimulus (2) × Electrode Region (7), and identified significant interactions by group in the factor waveform data. Post-hoc corrected t-tests including Tukey’s Honestly Significant Difference Test were performed when the omnibus RMA indicated significant interactions between group and within-subject variables such as stimulus (frequent or target) and electrode site. ERP variables that were significantly different between snoring children and non-snoring controls were entered into a stepwise multiple regression to determine which ERP elements significantly predicted scores on the CPRS-R: L.

Source Localization—Scalp potential source estimates were modeled using the GeoSource © imaging software (Electrical Geodesics, Inc., Eugene, OR). Investigators used a minimum-norm least squares solution (MNLS) and a finite difference model with the LAURA (local autoregressive average) constraint (Grave de Peralta Menendez *et al.*, 2004) to derive source locations based on the Montreal Neurological Institute probabilistic magnetic resonance image (MRI). Settings included weighting per location, truncated singular value decomposition (TSVD) regularization at 10^-3, and the radius of influence at 12.2mm (Frishkoff *et al.*, 2009). To compute estimates of the anatomical source activity, investigators focused on time points of maximal amplitude peaks from components of the temporal PCA. The source estimates contributing to the peaks for factors exhibiting significant differences by group are illustrated in the Results section.

Analysis of PSG Data

Overnight sleep studies were performed on all participants to rule out sleep disorders and—for those individuals in the control group—confirm the absence of snoring. Investigators tested the null hypothesis that $\mu_{SNORE} = \mu_{CONTROL}$ for sleep variables such as percent total sleep time (TST) in each sleep stage; number of respiratory, spontaneous, and total arousals; apnea/hypopnea index (AHI); and oxygen saturation using multiple un-paired Independent Samples t-tests.

Analysis of Behavioral Data

Independent Samples t-tests were used to examine standardized scores from the screening instruments and demographic parameters to ensure there were no differences between groups in potential confounding variables such as body mass index (BMI) or estimated intelligence quotient (using the standardized score from the PPVT-III as a proxy). Investigators tested the null hypothesis that $\mu_{SNORE} = \mu_{CONTROL}$ using standardized scores for the various domains of the CPRS-R: L and the Visual Attention subtest of the NEPSY. These served as the dependent variables for Independent Samples t-tests. Analyses were conducted to investigate significant differences between groups (Snoring versus Control). Variables on which the two groups were found to significantly differ were related to ERP data using stepwise multiple regression to determine if ERP differences could predict measures of behavior. An alpha level of 0.05 was used to determine significance for all statistical results including post-hoc and planned tests. Greenhouse-Geisser corrections were applied to all tests.

RESULTS

ERP PCA and RMA Results

Spatial PCA identified seven factors that accounted for 77.618% of the total variance in topographic distribution of activation. The resulting electrode groupings are illustrated in Figure 2. Using those electrode groupings, the temporal PCA was performed, producing six temporal factors which accounted for 87.713% of the total variance in the model. The RMA was then performed using the factor weights from the temporal PCA as the dependent variable. Factors 1 and 5 were the only temporal factors to exhibit significant main effects of group or interactions by group.

The group*stimulus interaction was significant for Factor 1 ($F = 5.194$, $p = 0.028$) that peaked at 844 ms post-stimulus onset. Post hoc analyses indicated that there was no significant difference in the brain responses of snorers to target versus frequent stimuli. However, significant differences were noted between responses to stimuli in controls ($t = -2.101$, $p = 0.043$). Additionally, there was a significant difference in how snoring versus control children processed the frequent tone at approximately 844 ms ($t = -2.101$, $p = 0.042$).

There was a significant group*electrode region interaction for Factor 5 ($F = 4.915$, $p = 0.002$). Factor 5 had a peak at approximately 124 ms post –stimulus onset. Post hoc analyzes identified significant effects at two electrode regions. Control children exhibited increased ERP amplitude over electrode region 4, a centrally located region ($t = 3.792$, $p = 0.001$). Snoring children exhibited increased ERP amplitude over electrode region 6, a right temporal region ($t = -3.482$, $p = 0.001$). There were no significant differences between groups in the number of correct responses during the oddball task or in the reaction time for correct responses.

Source Localization Results

Source localization solutions derived from topographical electrical activity and averaged by group are shown in Figures 3 and 4. In these topographic maps, one can see the statistically significantly increased activation at right temporal leads in snoring children compared to the more central activation recorded in non-snoring control children. Source localization was performed in GeoSource using this averaged brainwave data and produced the solutions illustrated in Figure 3. For snoring children, the estimated source generator in response to target stimuli was in the temporal lobe (specifically Brodmann area 22 in the superior temporal gyrus). The estimated source generator in response to the frequent stimuli was in the temporal lobe (Brodmann area 38 in the superior temporal gyrus). For control children, the estimated source generator in response to the target stimuli was in the precuneus of the parietal lobe (Brodmann area 31). The estimated source generator in response to the frequent stimuli for control children was located within the temporal lobe (Brodmann area 38 in the superior temporal gyrus).

Figure 4 illustrates the average activity for both groups at 844ms post-stimulus onset, which is the latency of the peak of maximal activation for Factor 1. The significant difference in activation patterns for frequent versus target stimuli can be seen for children in the control group in the source localization. For snoring children, the estimated source generator in response to target stimuli was in the frontal lobe (specifically Brodmann area 11 in the orbital gyrus). The estimated source generator in response to the frequent stimuli was in the frontal lobe (Brodmann area 10 in the medial frontal gyrus). For control children, the estimated source generator in response to the target stimuli was in the frontal lobe (Brodmann area 10 in the medial frontal gyrus). The estimated source generator in response to the frequent stimuli for control children was in the limbic lobe (estimated in the uncus of the amygdala).

PSG Results

Group means for relevant parameters from the overnight polysomnographic studies are shown in Table 2. There were no significant differences by group in any clinically relevant markers for SDB, including apnea/hypopnea index or oxygen saturation nadir. There were, however, group differences in the percentage of total sleep time spent in sleep stages 2 and 4. Occasionally snoring children spent less time in stage 2 ($t = -3.489$, $p = 0.001$) and more time in stage 4 ($t = 2.040$, $p = 0.048$) than their non-snoring counterparts.

Behavioral and Descriptive Results

Descriptive and demographic information for the two groups is shown in Table 1. There were no significant differences between groups for any variable, including BMI. Mean standardized scores on the PPVT-III and scaled scores for the NEPSY Visual Attention subtest are also shown in Table 1. There were no significant differences between groups on the PPVT-III, which was used as a proxy for IQ, or on the NEPSY Visual Attention scaled scores, which was used as a standardized assessment for attention. Rarely snoring children scored significantly higher than controls on 4 subscales of the CPRS-R: L : the Conner's Global Index for restlessness and impulsivity ($t = 2.314$, $p = 0.028$); the cognitive problems/inattention subscale ($t = 2.292$, $p = 0.028$); the DSM-IV-based subscale for the ADHD inattentive subtype ($t = 2.647$, $p = 0.013$); and DSM-IV-based total index for the ADHD combined subtype ($t = 2.402$, $p = 0.023$).

The stepwise multiple regression analyses indicated that two ERP variables from Factor 1 significantly predicted scores on the CPRS-R:L. The factor weights corresponding to activation over electrode region 4 (including parietal electrode sites) significantly predicted scores on the cognitive problems/inattention subscale ($F = 4.655$, $p = 0.037$); the anxious/shy subscale ($F = 4.586$, $p = 0.038$, adjusted R squared = 0.077); and the ADHD index ($F = 4.098$, $p = 0.049$, adjusted R squared = 0.067). The factor weights corresponding to activation over electrode region 3 (including central and parietal electrode sites) significantly predicted CPRS-R:L scores on the perfectionism subscale ($F = 5.131$, $p = 0.029$, adjusted R squared = 0.088).

DISCUSSION

ERP Results

Current ERP experiments show the presence of altered neural processing in children who snore occasionally and who otherwise have normal sleep studies. Indeed, the oddball task was more cognitively demanding for the rarely snoring children, who also exhibited more delayed and effortful processing. In contrast, control children processed the tones more quickly, engaging higher brain regions such as the precuneus at an earlier latency than snorers. At 124 ms post-stimulus, control children exhibited greater activation in attention-related central-parietal brain regions whereas snorers exhibited greater activation in the right temporal region, a region involved in pure tone discrimination. By 124 ms post stimulus, controls had already graduated to higher cognitive processes, while rare snorers were still engaged in basic sensory processing. Snoring children exhibited higher amplitude frontal activation than controls at 844 ms, indicating that once frontal processing occurred in rarely snoring children it required more effort than in control children. At this latency, children in the control group had less frontal activation and were showing activation in memory consolidation areas such as the amygdala—activation the rarely snoring children lacked.

Of note, no significant differences occurred between rarely snoring and non-snoring children on behaviorally observable phenomena such as the number of correct responses or the average reaction time for correct responses during the oddball task. It is our belief that rarely

snoring children may be able to perform as well as the non-snoring children by engaging more cognitive resources (Molfese et al., 2008). Our findings are consistent with previous reports in adults, suggesting that the volitional attention resources allocated to the processing of novel stimuli are sufficient in subjects with OSA, but more effortful and delayed relative to controls (Gosselin et al., 2006a; Gosselin et al., 2006b), most likely as the result of a decrease in overall cognitive resources available for the task at hand. Furthermore, the increased susceptibility of the prefrontal cortex and hippocampus to the effects of sleep fragmentation and hypoxia (D Gozal et al., 2001a; E. Gozal et al., 2001c) associated with SDB could require reliance on suboptimal generators such as the cingulate, auditory, or parietal cortices (Gosselin, et al., 2006b).

Discussion of PSG Results

Analysis of PSG variables confirmed the initial hypothesis that rarely snoring children do not meet diagnostic criteria for clinically relevant SDB. The rarely snoring children in this study did not exhibit increased apnea or hypopnea frequencies than the controls. Notwithstanding, rarely snoring children experienced more behavioral problems than controls according to parental reports. This suggests that snoring—however infrequent—is linked to increased morbidity, and that current analytical methods used to score overnight sleep studies are not sufficiently sensitive to assess the overall impact of snoring on neuropsychological processes of children.

There was a somewhat unexpected finding upon analysis of PSG data. Rarely snoring children exhibited a decreased percentage of total sleep time in stage 2 of non-rapid-eye-movement (NREM) sleep and an increased percentage of total sleep time in stage 4 of NREM sleep. We are unclear as to the significance of such findings.

Discussion of Behavioral Results

The hypothesis that snoring children would score significantly higher on subscales of the CPRS-R: L, thereby indicating increased behavioral problems, was also confirmed. Rarely snoring children scored higher on CPRS-R: L subscales for restlessness, cognitive problems/inattention, ADHD inattentive subtype, and ADHD combined subtype, similar to previous reports (Wei et al., 2007). Approximately one half of the snoring children scored one standard deviation or more above average on one or more subscales. In fact, most who scored above one standard deviation on one subscale scored high on several subscales.

Stepwise multiple regression findings supported the hypothesis that ERPs provide predictive markers for behavioral differences among the two study groups. For Factor 1, activity at electrode region 4 (including central and parietal electrode sites) elicited by target tones from the oddball task significantly predicted scores on the cognitive problems/inattention, anxious/shy, and ADHD indices of the CPRS:R-L. The parietal lobe contributes to nonverbal working memory (Wager & Smith, 2003) which could account for the accurate prediction of scores on the cognitive problems/inattention, perfectionism and ADHD subscales. Activation at prefrontal-central electrode sites could explain the relationship between this electrode region and the anxious/shy subscale, which could incorporate internalizing or inhibiting behaviors. It is interesting to note that the group that showed no activation of the amygdala on source localization exhibited higher scores on the anxious/shy subscale. However, this difference was not statistically significant. The finding that 2 ERP variables can predict scores on subscales of the CPRS-R:L is particularly important given the general lack of bio-physiological assessments in psychological diagnostics, especially considering the great difficulty in assessing complex behaviors. The ability for a physiological assessment to account for nearly 10% of the variance of a behavioral

assessment is not trivial. Such results underscore the argument that ERPs hold significant promise as quick, safe, and relatively inexpensive diagnostic tools.

Study Limitations and Strengths

Reliance on parental report could have introduced bias. However, parental report of snoring is one of the most robust markers of neurocognitive impairment in studies of pediatric SDB (Beebe, 2006), suggesting the existence of a spectrum of snoring severity being associated with parallel changes in behavioral patterns. The lack of longitudinal follow-up to investigate long-term effects of non-habitual snoring in children is clearly a limitation of the present study and will require additional studies in the future. We did not incorporate analyses of genetic or proteomic markers such as Apolipoprotein E alleles or C reactive protein, which are altered in children with SDB, particularly in those who are most adversely affected by the underlying SDB (D Gozal *et al.*, 2007a; D. Gozal *et al.*, 2007b; Tauman *et al.*, 2004).

The strengths of this study are its prediction and explanation of real-life, behaviorally observed phenomena--such as the increased behavioral and attention problems previously reported in children with snoring and/or SDB—by objectively measured electrophysiological markers (Brietzke & Gallagher, 2006; O'Brien et al., 2004a; O'Brien et al., 2004b). Furthermore, there are many applications for this non-invasive and relatively inexpensive technique, which is well matched to the current need for new diagnostic and evaluative procedures in pediatric sleep medicine and research. Future studies are needed to link these results to brain morphology and more complex—and perhaps reciprocal—interactions between the brain, other systems such as the cardiovascular, metabolic, respiratory, and immune systems, and the complex neuropsychological process and behaviors that develop in childhood.

Conclusions

Children who snore are not likely to "grow out of it" over the course of their development (Lofstrand-Tidestrom & Hultcrantz, 2007). In their 2008 review, Giordani and Chervin argue that SDB severity is not directly related to the degree of neurocognitive and behavioral impairment when assessed by polysomnography. For example, children with milder forms of SDB could have more behavior problems than children with overt OSA (Giordani & Chervin, 2008). The authors concluded that new measures should be developed and closely examined to further elucidate the relationship(s) between SDB and neurobehavioral morbidity. The present investigation represents one attempt in this direction.

Over 250,000 children are surgically treated for obstructive sleep apnea (the most severe form of SDB) each year in the United States alone (Brietzke & Gallagher, 2006). Evaluation and treatment of pediatric SDB is a major public health concern. Primary snoring, once considered important only insofar as it was a hallmark of more severe disease, is now being investigated as a milder form of SDB that may require treatment. Standard polysomnographic measures should no longer be considered as accurate predictors of neuropsychological morbidity in children who snore (Giordani and Chervin, 2008). Indeed, none of the children in this study met polysomnographic intervention criteria, and yet, substantial behavioral and ERP differences emerged when compared to control children. Rarely snoring children exhibited altered neural functioning, including delayed and more effortful processing and a reliance on suboptimal cognitive generators. Thus, children with a history of snoring of any frequency or severity should be excluded from any normative control group. More research is clearly needed to determine mechanisms underlying increased neurobehavioral susceptibility to the presence of snoring (Giordani & Chervin,

2008; D Gozal et al., 2007a; Kuehni et al., 2008). Coupled with behavioral assessments, ERPs may prove useful in identifying which children would benefit from therapeutic interventions to reduce or eliminate snoring, and serve as useful tools to monitor treatment outcomes.

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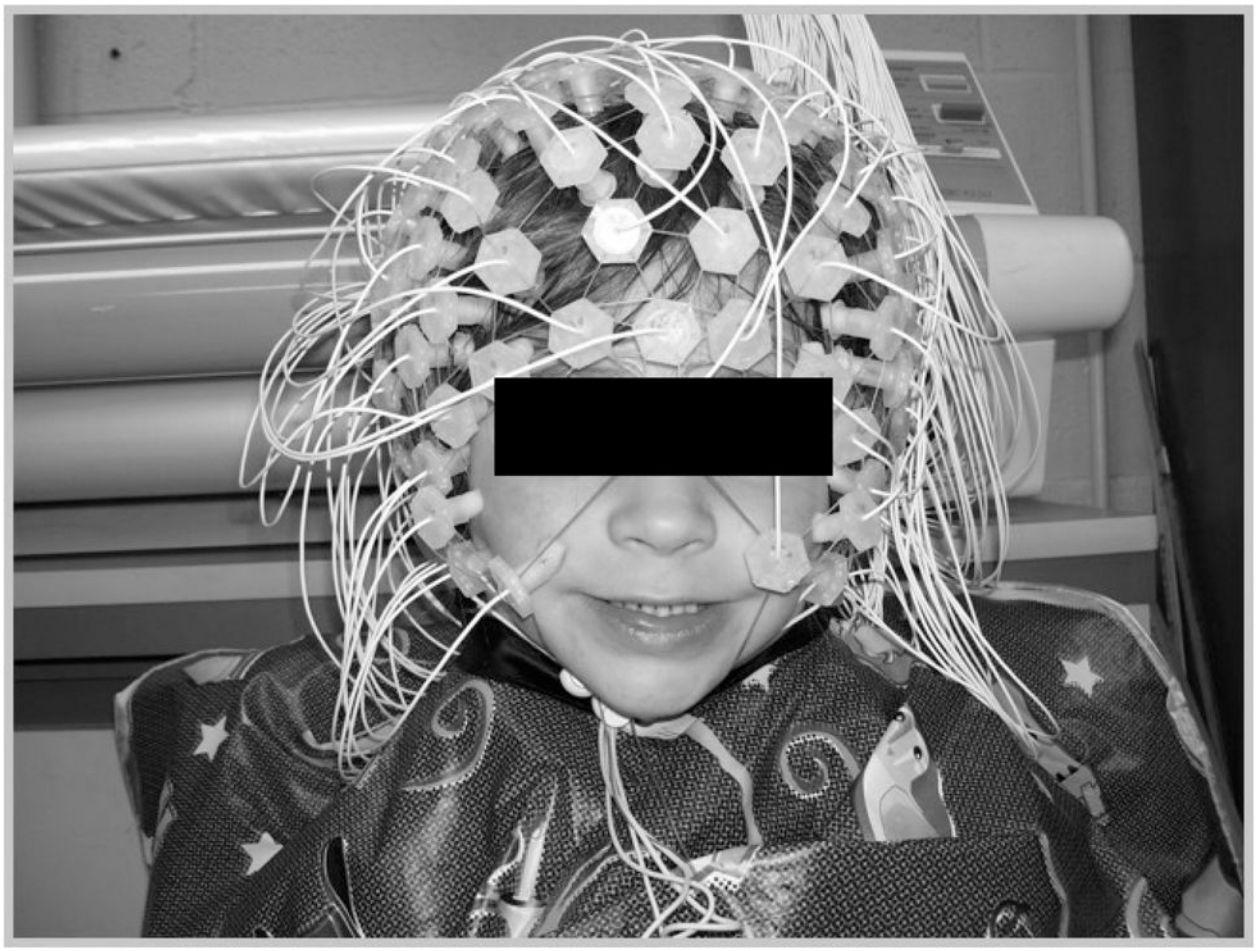

Figure 1.
Photograph of participant in 128-electrode net.

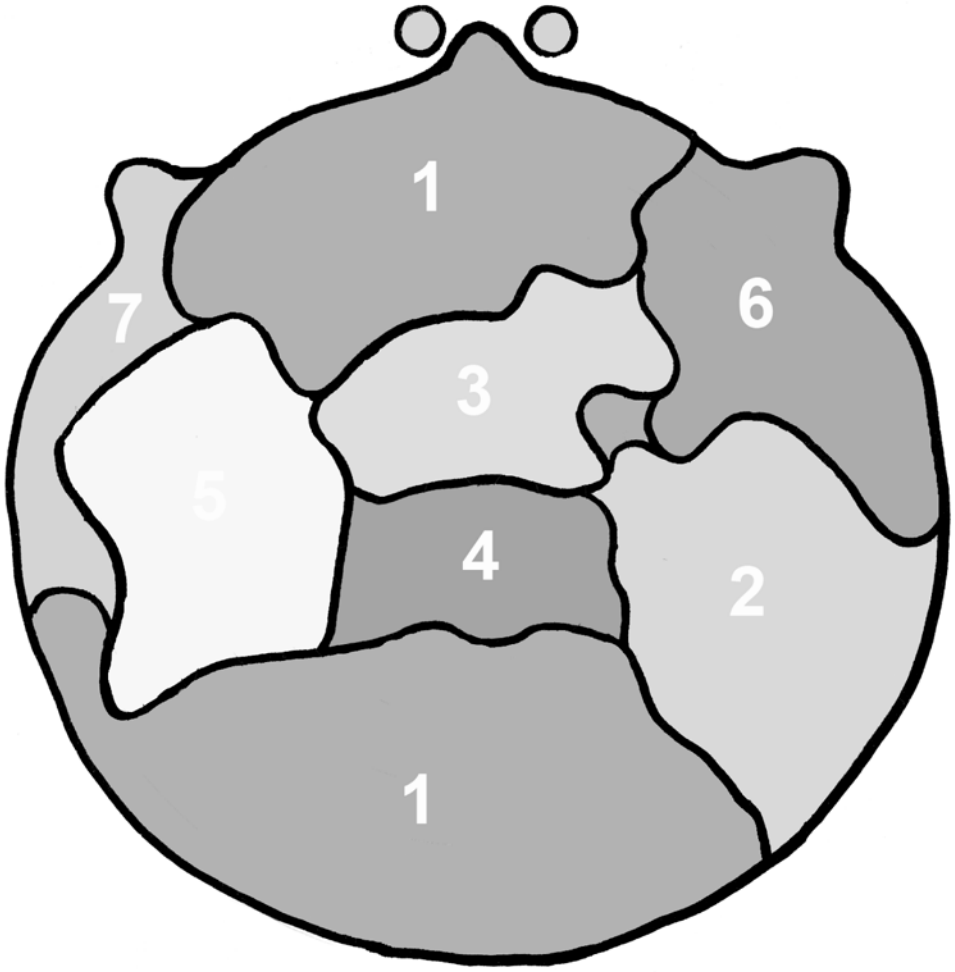

Figure 2.
Illustration of electrode groupings obtained from spatial principal components analysis.

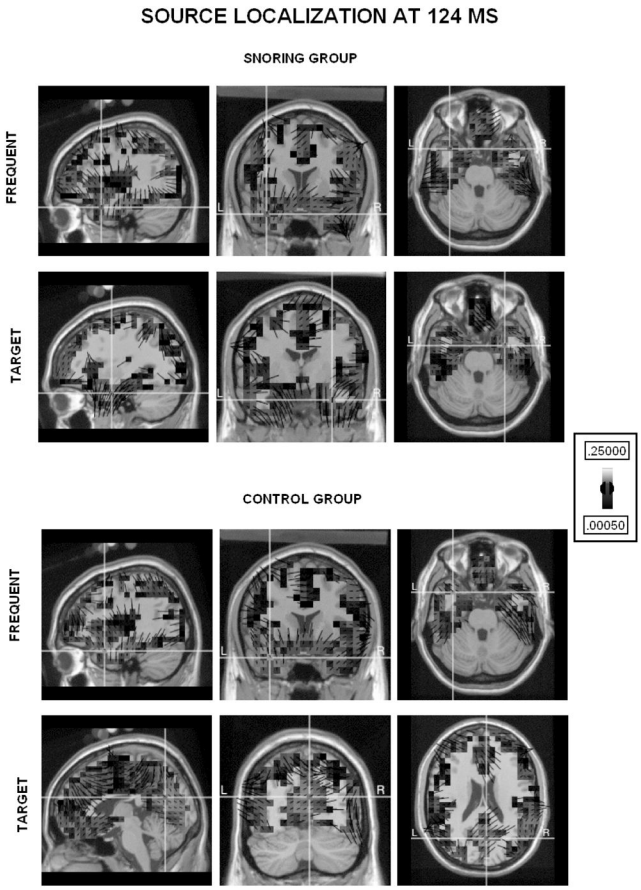

Figure 3.

Source localization by group at 124 milliseconds (peak latency of temporal Factor 5). The sagittal view is on the left, coronal is in the center, and axial is on the right. For snoring children, the estimated source generators in response to target and frequent stimuli were in the temporal lobes. For control children, the estimated source generator in response to the target stimuli was located within the precuneus of the parietal lobe while the location shifted to the superior temporal gyrus of the temporal lobe in response to the frequent stimuli.

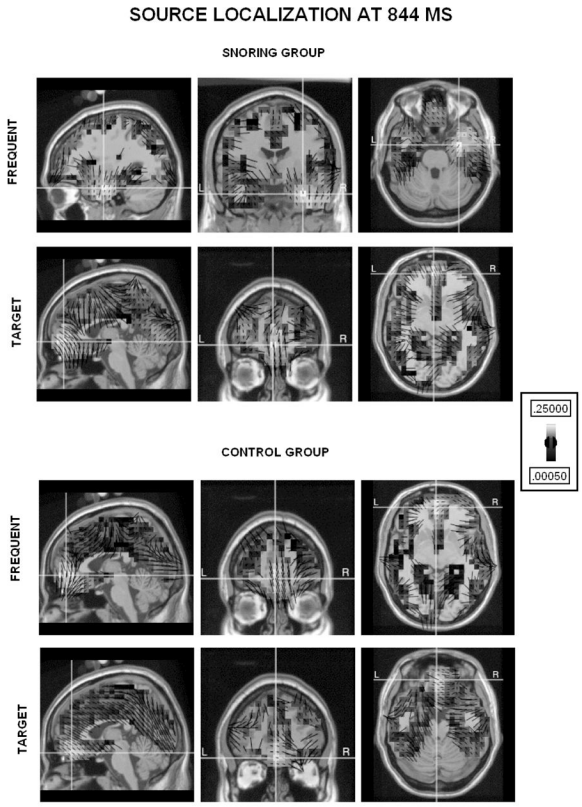

Figure 4.

Source localization by group at 844 milliseconds (peak latency of temporal Factor 1). The sagittal view is on the left, coronal is in the center, and axial is on the right. In snorers, the estimated source generator in response to target and frequent stimuli was located in the frontal lobe. In controls, the estimated electrical source originated in the frontal lobe for target stimuli and in the amygdala for frequent stimuli.

Table 1

Demographic and Behavioral Variables for Rarely-Snoring and Non-Snoring Children

Variable	Snoring Group	Control Group
Age	6.9195 ± 1.2443	6.9186 ± 1.2069
BMI	17.5628 ± 4.1205	15.9886 ± 1.3172
PPVT-III	108.5882 ± 12.3999	106.4667 ± 13.0541
NEPSY Visual Attention	10.9545 ± 3.1088	10.5714 ± 3.2950

Note. Both groups have n=22. Values given in means ± SD. PPVT-III = Standardized score on Peabody Picture Vocabulary Test-III. NEPSY Visual Attention = Scaled score on NEPSY Visual Attention subtest.

*
$p<0.05$.

**
$p<0.01$.

Table 2

Polysomnographic Variables for Rarely-Snoring and Non-Snoring Children

Variable	Snoring Group	Control Group
Apnea-Hypopnea Index	0.823 ± 0.866	0.850 ± 0.444
Apnea Index	0.627 ± 0.560	0.741 ± 0.386
Lowest Oxygen Saturation	93.619 ± 2.617	93.364 ± 2.682
% Stage 1	5.241 ± 2.725	4.923 ± 2.418
% Stage 2	45.427 ± 6.912 *	52.086 ± 5.690 *
% Stage 3	6.446 ± 2.823	5.686 ± 2.582
% Stage 4	22.064 ± 5.489 **	18.686 ± 5.494 **
% REM	19.841 ± 4.720	17.827 ± 4.178
Total Sleep Time	490.386 ± 39.490	480.318 ± 55.962
Arousal Index	8.88 ± 4.268	10.85 ± 5.415

Note. Both groups have n=22. Values given in means ± SD.

* $p<0.05$.

** $p<0.01$.