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# Sleep-Disordered Breathing Affects Auditory Processing in 5–7 Year-Old Children: Evidence From Brain Recordings

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## Abstract

Poor sleep in children is associated with lower neurocognitive functioning and increased maladaptive behaviors. The current study examined the impact of snoring (the most common manifestation of sleep-disordered breathing) on cognitive and brain functioning in a sample of 35 asymptomatic children ages 5–7 years identified in the community as having habitual snoring (SDB). All participants completed polysomnographic, neurocognitive (NEPSY) and psychophysiological (ERPs to speech sounds) assessments. The results indicated that sub-clinical levels of SDB may not necessarily lead to reduced performance on standardized behavioral measures of attention and memory. However, brain indices of speech perception and discrimination (N1/P2) are sensitive to individual differences in the quality of sleep. We postulate that addition of ERPs to the standard clinical measures of sleep problems could lead to early identification of children who may be more cognitively vulnerable because of chronic sleep disturbances.

From birth, and through preschool and early school age, children spend as much or more time asleep than awake, and the amount of sleep they require clearly exceeds the physiological sleep requirements of young adults (Mindell, Owens, & Carskadon, 1999), possibly due to the role sleep plays in early brain development and learning (Dahl, 1996; Stickgold, 2001). However, most assumptions about the specific role of sleep have been developed from experimental work in adults involving sleep deprivation or sleep disorders (sleep apnea, narcolepsy, etc.). Meta-analysis of these studies revealed remarkably consistent results, namely that insufficient sleep leads to reduced levels of alertness, along with increases in perceptual and cognitive distortions, decreased reaction times, and changes in the regulation of affect (Pilcher & Huffcutt, 1996; Dahl, 1996). Neuroimaging studies further demonstrated that even short-term sleep deprivation in healthy young adults greatly impacts prefrontal cortical functions, decreasing flexible thinking, verbal fluency, memory for temporal order, and inhibition (Braun, et al 1997; Horne, 1988, 1993; Wimmer, et al 1992; Harrison & Horne, 1997, <sup>1998</sup>, <sup>1999</sup>, <sup>2000</sup>; Dorsey, et al., 2000; Thomas, et al., 1993, 1998; Breimhorst, Falkenstein, Marks, & Griefahn, 2008).

Experimental studies of total or partial sleep deprivation in children are very limited and suggest a wide range of outcomes. One night of total sleep deprivation in adolescents (11–14 years old) led to decreased performance on the Wilkinson Addition Test and Williams Word Memory Test (Carskadon & Dement, 1981). However, partial sleep restriction (4 hours of sleep in one

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night) failed to produce significant changes in psychomotor performance in children ages 11 to 13 years (Carskadon. Harvey, & Dement, 1981). In a more recent study of 16 children 10–14 years of age, sleep restriction to 5 hours during a single night in the sleep laboratory resulted in decreased performance on tests of verbal creativity and on Wisconsin Card Sorting Test, even though performance of routine tasks remained relatively preserved (Randazzo, et al., 1998).

Observational studies in pediatric populations reported similar findings. Sleep-deprived children often present behavioral and cognitive symptoms that resemble those reported in attention deficit hyperactivity disorder (Dahl et al., 1991; Dahl, 1996; Kennedy & Meyer, 1996; Picchietti, 1994; Guilleminault, et al., 1982). Using actigraphy data obtained 6 to 13-year-old children during a regular school week, Steenari and colleagues (2003) demonstrated that greater sleep duration and better quality were associated with higher performance on auditory and visual working memory tasks. Disturbances of sleep at an early age also impact later developmental outcomes. In a longitudinal study of 490 children from 4 to 15 years of age, Gregory and O'Connor (2002) observed that sleep problems (nightmares, atypical sleep duration, sleepwalking, etc.) at 4 years were associated with behavioral, emotional (e.g., depression and anxiety) and attention problems in mid-adolescence. Interestingly, early depression and/or anxiety did not predict later sleep problems.

Although total sleep deprivation is not common in children's daily life, a host of sleep disturbances leading to altered sleep may occur in many households (NSF 2004), and may impose detrimental and profound influences on child development (see Bass et al, 2004 for a review). One of the most common problems is sleep-disordered breathing (SDB). SDB consists of a spectrum of conditions associated with increased upper airway resistance during sleep that encompass habitual snoring all the way to the presence of recurring partial (hypopnea) or complete upper airway collapse (apnea) (Archbold et al., 2004). These events may then lead to repeated episodes of hypoxia (Gozal 1998,Lewin et al 2002), as well as fragmentation of sleep (Goh et al, 2000). By some accounts, habitual snoring occurs in 6–27% of the population (Carroll et al, 1995). In a recent epidemiological survey of children in Louisville, 11.7% of all children ages 5–7 years reported frequent and loud snoring on a regular basis (O'Brien et al, 2003).

Existing data indicate that children with SDB experience sleep disruption, intermittent hypoxia and hypercarbia, and maladaptive daytime behavior and reduced academic performance (Beebe & Gozal, 2002; Gozal, 1998; Gozal & Pope, 2001, Gozal, et al., 2001) as well as lower auditory and visual attention and mental flexibility (Archbold et al, 2004). However, many of these findings originated from samples of clinically referred children who met the criteria for the more severe forms of SDB. Of note, milder forms of SDB can be associated with behavioral disturbance and cognitive impairment (Chervin et al., 2001, Gottlieb et al., 2004; O'Brien et al., 2004). In a review of SDB effects in children, Blunden et al. (2001) reported that SDB results in the primary deficit of attention that in turn leads to reduced performance on other cognitive tasks and lower learning capacity. Therefore, critical assessment of the neurocognitive consequences associated with more modest sleep disturbances due to snoring in young children, is of increasing clinical, social, and educational relevance.

Measures of electrical activity of the brain, such as event-related potentials (ERPs) are increasingly being used as a tool to obtain objective measurements of the integrity of cognitive processes (Johnstone et al., 2001) and for documenting neural dysfunction associated with sleep problems (Walsleben, et al., 1989; Ayalon & Peterson, 2007). ERP is a portion of the electroencephalogram (EEG) that is time-locked to the onset of a stimulus (e.g., sound, picture) and reflects subtle psychophysiological processes that may not always be observable using traditional behavioral assessments (Molfese, Molfese & Kelly, 2001).

Prior studies in adults with chronic sleep problems (obstructive sleep apnea, OSA) revealed delayed processing speed (longer latencies for N2 and/or P3 response, Walsleben et al., 1989; Sangal & Sangal, 1997) and reduced attention (decrease in N2-P3 amplitude; Rumbach et al., 1991; Kingshott et al., 2000), although these ERP characteristics may improve with treatment (Corsi-Cabrera et al., 1999). Pressman et al. (1982) reported that acute sleep deprivation resulted in increased peak-to-peak amplitudes of auditory N1-P2 and P2-N2 regions, suggesting increased processing of basic sensory information (but see Regestein et al., 1993 for the opposing view). Johnstone et al (2001) reported similar attenuation of the P3 amplitude in children with OSA and observed that treatment resulted in the normalization of the ERPs; however, treatment removal returned P3 values to the original atypical levels.

Sleep problems in younger participants may have different and possibly unique effects on their neurocognitive processes. In particular, examining the efficiency of early information processing stages may be informative about the basic mechanisms whose proper functioning is required for successful performance of more advanced cognitive tasks. In the past, a basic ability to perceive differences in speech stimuli (CV syllables) have been predictive of a host of later developmental outcomes (Molfese & Molfese, 1985; Molfese, 2000), suggesting that perceptual efficiency is critical for proper cognitive development (Molfese & Molfese, 1997).

Therefore, the purpose of the current study was to examine the relationship between sleep, cognitive and psychophysiological characteristics in children 5–7 years of age from the community with reported snoring. This approach provided an opportunity to identify substantially new information concerning the impact of sleep disturbances on the developing neurocognitive system as well as the practical impact of the degree of SDB on the child's ability to process information typically involved in educational and other learning activities.

### Method

#### **Participants**

The study was approved by the University of Louisville Human Studies Committee and the Jefferson County Public Schools (JCPS) Board. Parents of all children enrolling in the 1st grade of the JCPS system were invited to complete a previously validated detailed questionnaire about their child's sleeping habits (Gozal, 1998). In addition to demographic information and significant medical history of the child, questions included whether the child had difficulty initiating sleep, restless sleep, enuresis, apnea, cyanosis during sleep, snoring and, if so, the severity of the snoring. The responses were graded as "never", "rarely" (once per week), "occasionally" (twice per week), "frequently" (3–4 times per week) and "almost always" (>4 times per week).

Thirty-nine otherwise healthy children (18 females) were identified randomly as habitual snorers based on the responses to the questionnaire and were invited to the Pediatric Sleep Center at Kosair Children's Hospital, Louisville, Kentucky to participate in the study. Thirty-five children age 5.3–7.5 years (M=6.5+/-0.5 years; 18 females) agreed to participate. Parental informed consent and child assent, in the presence of a parent, were obtained prior to the study procedures. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Five children were left-handed (LQ=-0.63 +/- 0.27), one child was ambidextrous (LQ=0), and 21 children were right-handed (LQ=0.72 +/- 0.21). Handedness data for the remaining eight children were obtained by parental report and observation and placed them into the right-handed group.

#### Cogntive assessment

The cognitive assessment included measures of attention, memory, and language abilities (NEPSY; Korkman, Kirk, & Kemp 1998).

#### **Polysomnographic Assessment**

A standard overnight multichannel polysomnographic evaluation was performed at the Sleep Medicine Center of Kosair Children's Hospital. Children were studied for up to 12 hours in a quiet, darkened room with an ambient temperature of 24°C in the company of one of their parents. There was no adaptation night, and children were requested to be in bed with lights out occurring between 21:00 and 21:30 hours. No drugs were used to induce sleep. All studies were terminated when the children woke up for the day or at approximately 7:30 am if they were still sleeping, whether or not the studies were performed on a school night or a weekend. The following parameters were measured: chest and abdominal wall movement by respiratory impedance or inductance plethysmography, heart rate (ECG), air flow was monitored with a sidestream end-tidal capnograph which also provided breath-by-breath assessment of end-tidal carbon dioxide levels (PETCO<sub>2</sub>; BCI SC-300, Menomonee Falls, WI), a nasal pressure transducer, and a thermistor. Arterial oxygen saturation (SpO<sub>2</sub>) was assessed by pulse oximetry (Nellcor N 100; Nellcor Inc., Hayward, CA), with simultaneous recording of the pulse waveform. The 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 commercially available polysomnography systems. Tracheal sound was monitored with a microphone sensor (Sleepmate, VA) and a digital time-synchronized video recording was performed.

#### **Sleep Variables**

Sleep architecture was assessed by standard techniques (Rechtschaffen & Kales, 1968). Arousals were defined as recommended by the American Sleep Disorders Association Task Force report (Sleep Disorders Atlas Task Force, 1992) and included respiratory-related (occurring immediately flowing an apnea, hypopnea or snore), technician-induced and spontaneous arousals. Arousals were expressed as the total number of arousals per hour of sleep time. The apnea index (AI) was defined as the number of apneas (cessation of airflow or reductions in airflow >90%) per hour of total sleep time (TST). Hypopneas (partial obstructions) were defined as a decrease in nasal flow of  $\geq$ 50% with a corresponding decrease in SpO<sub>2</sub> of  $\geq$ 4% and/or arousal (Montgomery-Downs et al., 2006). The apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of TST and quantified the overall severity of the participant's sleep disruption and oxygen desaturation. Additional measures included the mean oxygen saturation, as measured by pulse oximetry (SpO2), together with SpO2 nadir, and the mean and peak end-tidal carbon dioxide tension ( $P_{FT}CO2$ ). Central, obstructive and mixed apneic events were counted. Periodic leg movements (PLM) during sleep were scored if there were at least 4 movements of 0.5 to 5 seconds duration, and between 5 and 90 seconds apart. A PLM index of  $\geq$ 5 per hour of sleep is generally considered to be rare in normal children (Diagnostic Classification Steering Committee, 1990).

#### **ERP procedures**

**Stimuli**—Six computer-generated consonant-vowel (CV) syllables were used (/ba/, /da/, /ga/, /bu/, /du/, /gu/). These stimuli began with an initial consonant transition that was 50 ms in duration followed by a 250 ms steady state vowel (Cutting, 1974). Each syllable was composed of five formants. An initial upgliding (i.e., rising) second formant transition characterized the consonant sound portion of the /ba/ syllable while a falling second formant transition characterized the consonant portion of the /ga/ stimulus. The first and third formants of both

consonant sounds contained initial up-gliding components for the syllables. Each syllable was presented 25 times in random order. The sounds were presented through a speaker positioned 3 feet above the child's head. Volume was set at 75 dB SPL (A) as measured at the ear level. The intertrial interval varied randomly from 1400 to 2400 ms to prevent creation of expectation of stimulus onset and habituation effects.

**Electrodes**—A high-density sensor array of 128 Ag/AgCl electrodes embedded in soft sponges and arranged into a net (Geodesic Sensor Net, EGI, Inc., Eugene, OR) was used to acquire electrophysiological data. All impedances remained below 40 kOhms during the test session as evidenced by pre- and post-test impedance measures. Data were samples at 250 Hz with filters set to 0.1–30 Hz. During recording, all electrodes were referenced to Cz and then subsequently re-referenced to an average reference during data analysis. Net Station (v. 1.0, EGI, Inc.) was used to record the electrophysiological data.

**Procedure**—All participants were tested individually prior to or immediately following the sleep study. To help the children feel more comfortable during the test, they were offered to watch an age-appropriate video prior to and during the electrode net application. Once the child was seated comfortably in a chair or on a parent's lap, he/she was instructed to sit quietly and listen to the stimulus sounds. The stimulus presentation was controlled by Electrophysiological Graphical Imaging System (EGIS v. 2.2, EGI, Inc.).

**Analyses**—Following data collection, ongoing EEG for each participant was segmented on stimulus onset to include a 100-ms pre-stimulus interval (baseline) and a 700 ms post-stimulus interval. Segments contaminated by eye movement, eye blinks, or other motor artifacts were excluded from the analyses. The remaining trials were averaged individually for each condition and participant and re-referenced to the average reference. Electrodes identified as "bad" (signal exceeding 70  $\mu$ V on 10% of the trials) were replaced by interpolating their data from immediately adjacent electrodes. Trials with more than 20 bad electrodes were excluded from the analysis. For a participant's data set to be included in the overall analysis, the averages for each condition had to be based on a minimum of 10 trials

Following baseline correction, data from 128 electrodes were clustered into 10 regions by averaging the data for electrodes within five anatomical regions for each hemisphere –frontal, central, parietal, occipital, and temporal (see Figure 1). This approach reflected anatomically based boundaries and represented a modification of the clusters initially proposed by Curran (1999) and used successfully in previous studies (Mayes et al., 2005;Key et al, 2006). The purpose of the clustering procedure was to reduce the number of variables and therefore lower the experiment-wise error.

The clustered data were submitted to a temporal principal components analysis (PCA) using a covariance matrix and Varimax rotation. The PCA identified intervals of high variability in ERPs (i.e., factors). The rotated factor scores served as dependent variables in a repeated measures ANOVA that was used to identify the possible causes of the variability. The analysis design included Consonant (3: /b/, /d/, /g/) × Vowel (2: /a/, /u/) × Electrode Region (5: frontal, central, parietal, occipital, and temporal) × Hemisphere (2: left, right) variables. The Greenhouse-Geisser correction was applied where appropriate

### Results

#### Sleep and behavioral characteristics

Of the 35 subjects who completed the study, 3 (8.5%) had clinically significant sleepdisordered breathing (M AHI=7.94 +/- 1.58/hour total sleep time) meeting the criterion for clinical obstructive sleep apnea (defined as AHI>5/hour of total sleep time), while the

remaining 32 children demonstrated sub-clinical levels of SDB (AHI = 0.12 to 3.37/ hour of total sleep time, M=0.94+/-0.80). These results are consistent with the reported prevalence rate for SDB in pediatric populations (O'Brien et al., 2003). There was no correlation of AHI with age (p>.20), however, the apnea index decreased with increasing age (r=-.468, p=.005). Examination of the possible associations between the AHI and cognitive functioning did not result in any significant correlations except for the Speeded Naming scaled scores, in which greater AHI was associated with better scores (r=.357, p=.038). A detailed summary of the participant sleep and cognitive characteristics is presented in Table 1. Of note, the cumulative oxygen desaturation indices and arousal indices were within the normal limits in this group with very mild SDB (Mongtomery-Downs et al., 2006).

#### ERPs to speech sounds

The PCA identified four factors that accounted for 80.26% of the total variance. Factor 1 accounted for 26.77% of the variance and described a region of variability between 480–700 ms, with the maximum at 640 ms. It corresponded to the late slow wave (SW) of the ERP. Factor 2 overlapped the P3 region. It accounted for 20.02% of the variance in the 332–476 ms region with the maximum at 412 ms. Factor 3 accounted for 17.06% of the variance and was associated with the P1-N1 complex occurring between 64–192 ms. It reached a point of maximum variability at 132 ms. Factor 4 accounted for 16.40% of the variance and corresponded to the P2-N2 component in the 204–332 ms interval with maximum variability noted at 272 ms.

ANOVA analyses identified a number of main effects and interactions involving consonants and/or vowels for three of the four factors. Significant interactions were followed with tests for simple effects. Syllable discrimination was evident shortly after stimulus onset (Factor 3), as reflected by the Consonant × Vowel interaction (F(2, 68)=4.525, p=.017, eta sq=.117, observed power =.726). More specifically, consonant differences were reflected in more positive amplitudes for /gu/ vs. /bu/ (t(34)=2.996, p=.005; see Figure 2), while vowel differences were associated with more positive amplitudes for /gu/ vs. /ga/ (t(34)=2.568, p=. 014).

In the 204–332 ms window (Factor 4), significant effects included a main effect of Vowel (F (1, 34)=11.87, p=.002, eta sq=.259, power=.917) and a Consonant × Electrode × Hemisphere interaction (F(8, 272)=2.742, p=.032, eta sq=.075, power=.738). Post-hocs revealed that differences were due to more positive amplitudes for /u/ vs /a/ sounds (t(34)=3.445, p=.002). While there were no significant discrimination effects for the consonants at any electrode location, the interaction was due to frontal hemisphere asymmetry present for /g/ sounds with more positive amplitudes observed over the left than right hemisphere (t(34)=2.644, p=.012).

In the 332–476 ms interval (Factor 2), ANOVA identified no significant effects involving vowels or consonants.

For the 480–700 ms range (Factor 1), variability in the brainwaves was attributed to the main effect of Vowel (F(1,34)=7.106, p=.012, eta sq=.173, power=.735) and interaction of Vowel x Electrode (F(4, 136)=3.900, p=.048, eta sq=.103, power=.530). Post-hocs indicated that /u/ sounds continued to elicit more positive amplitudes over temporal leads (t(34)=4.191, p<.0001; see Figure 3), while the reversed relationship was observed over the central scalp (t(34)=2.101, p=.043).

#### Sleep Characteristics, Cognition, and Speech Perception

Despite the relatively wide age range of the participants, there were no age correlations with the ERPs to speech sounds. Examination of correlations between sleep measures and ERPs

reflecting statistically significant speech differentiation indicated that higher AHI was associated with reduced (more positive) N1 amplitude to /bu/ responses (64–192ms; r=.414, p=.013). Because AHI is a composite index of both complete and partially obstructed breath events, individual contributions of apnea episodes were also examined. Apnea Index correlated with response to the syllable /ga/ (64–192ms; r=-.338, p=.047; higher AI = more negative N1) and /ga/-/gu/ contrast (r=-.356, p=.036, higher AI = smaller difference), as well as the with the P2 (204–332 ms) response to /a/-ending sounds (r=.359, p=.034; larger AI = larger P2). There were no significant associations between ERP measures and oxygen desaturation index or arousal index in this group of children with very mild SDB.

# Discussion

Previous research indicated that SDB in children is associated with several cognitive impairments (see Beebe, 2006 for a review). The present study assessed the impact of mild otherwise asymptomatic SDB on electrical brain activity associated with speech perception in a sample of young children who reported habitual snoring in a community based questionnaire survey. Consistent with the prior prevalence estimates, 8.5% (3/35) of the current sample met the criterion for sleep apnea (AHI > 5) among otherwise healthy habitually snoring children. Examination of the relationship between AHI and neurocognitive performance revealed no correlations with the NEPSY measures of attention or memory. However, children with higher AHI scored higher on the Speeded Naming subtest.

Although counterintuitive, the latter finding is consistent with prior reports of higher IQ scores and better vocabulary performance on WISC-III in 5-12-year-olds with more severe OSA (Owens et al., 2000). Similarly, Lewin et al (2002) reported that children with more severe OSA had fewer behavioral and emotional problems that those with the milder OSA (see also Kennedy et al., 2004). The lack of correlations with the attention measures may be due to our sample containing a larger proportion of children with very mild SDB, while prior studies reporting such associations included children with more severe degrees of SDB. It is also possible that no relation between sleep measures and the NEPSY scores was due to the young age of our sample whose cognitive skills are still emerging (Hill et al., 2006), although the latter is unlikely (O'Brien et al., 2003, 2004).

Examination of brain responses to speech sounds revealed discrimination of consonants and vowels in the typical time ranges, however, the exact characteristics of the ERP waveforms varied with the respiratory pattern characteristics during sleep, especially the apnea index. These results fit well with prior reports of no verbal deficits in children with SDB (Lewin et al. 2002; O'Brien et al, 2004), even though SDB may lead to reduced phonological processing skills (O'Brien et al, 2004).

It is particularly interesting that in our sample the composite AHI, traditionally used to determine clinical levels of sleep disturbance, showed fewer associations with the measures of brain functioning than the apnea index. This pattern of results may be due to the nature of the AHI as it represents a total number of apneas and hypopneas and is used as a guide for a clinician to recommend treatment. However, this threshold is rather arbitrary (O'Brien et al., 2004) and there is no single accepted cut-off for AHI in children. For example, Marcus & Carroll (1993) classified AHI < 1 event/hour of total sleep time as normal, while values >1 fell in the SDB category, while Gottlieb et al. (2004) and Hill et al (2006) used the cut-off of 4 or 5 events/ hour of sleep, respectively, for the SDB definition in their samples. This variability makes it difficult to compare results across studies. Nevertheless, a number of research studies have demonstrated that even modest pre-clinical levels of SDB may have a detrimental effect on cognition and behavior in children. Thus, the utility of AHI may increase through addition of other measures (e.g., oxyhemoglobin desaturation; O'Brien et al., 2004), even if there is a lack

of correlational data for oxygen desaturation and neurocognitive performance (Blunden et al, 2001).

In the present study, the apnea index appeared to have strong associations with the physiological measures of speech processing and discrimination, suggesting that repeated instances of complete upper airway obstruction during sleep might be a major contributor to the observed behavioral phenotype among children at the low end of the SDB severity spectrum. Apnea may impact brain functioning in multiple ways. One mechanism could be the increased blood CO2 levels. Although recent investigation by Bloch-Salisbury, Lansing, & Shea (2000) demonstrated that manipulating PETCO2 levels (within the normal range) in adult participants resulted in no changes in auditory N1-P2 amplitudes, future studies would need to examine whether frequent apnea episodes during sleep in children results in greater than typical variability in  $CO_2$  levels and/or whether the developing brain may be more susceptible to its adverse effects in a chronic, rather than acute setting. An alternative explanation is that numerous apnea episodes interrupt sleep and lead to increasing daytime sleepiness, the recognition of which may be difficult (Gozal et al., 2001 Gozal et al., 2009; O'Brien et al., 2004b; Tauman et al., 2004). In a recent study with adults, Cote et al (2003) reported reduced amplitudes of the auditory N1 following sleep fragmentation nights. However, non-obese children with obstructive sleep apnea appear to have a reduced propensity for sleep fragmentation (Gozal, Wang, & Pope, 2001; Goh, et al, 2000) and in our sample, increased apnea index was associated with increased rather than decreased amplitudes of N1 and P2. Recently, Wong et al. (2006) reported increased N1/P2 amplitudes in adults with predicted OSA (on the basis of a Multivariable Apnea Predication Index). Increased amplitudes suggest greater engagement of resources for early orienting to and detection of stimulus onset (N1) and perceptual analysis (P2) and may be indicative of increased attention allocation (Luck et al, 2000) to the auditory stimuli. Given that the stimuli in the current study were speech syllables, and the participants were asked only to listen to the sounds (i.e., no active discrimination required), one would expect that due to the simplicity of the task and familiarity of the auditory input, stimulus processing should be carried out nearly automatically. Evidence of increased brain activity associated with basic perceptual processing in children with higher apnea index may be indicative of greater effort and/or potential impairments in the system regulating attentional demands. Such findings are consistent with altered cognitive processing recently reported during an attentional task in adult patients using functional brain imaging approaches (Ayalon et al., 2009).

Although many of our findings fit well within the existing literature, the present study has several limitations. The current sample was representative of the community and this included only three children (8.5%) with clinically significant obstructive sleep apnea. Similarly, because of the selection criteria, all children in the study snored. In order to further extend our understanding of the impact of SDB on brain development and cognitive functioning, future studies would need to include children without any sleep concerns as well as those with severe SDB. Also, restricting the testing schedule to a particular time of day (e.g., morning) would allow to control for potential contributions of circadian factors and to examine whether the effects of snoring on neurocognitive functioning are more pronounced at a particular time of day. Finally, although post-hoc analyses in the current sample revealed no sex-related differences in ERPs to speech syllables, future studies should investigate whether SDB impacts neurocognitive functioning of males and females differently.

In summary, our findings are in line with previous evidence indicating that even mild SDB may be associated with alterations of brain functioning. However, we extended these observations to include previously unreported changes in basic perceptual processes that provide foundation for the development of higher-order functions such as attention and memory.

Previous clinical observations noted that sleep disruption in children with OSA may be less noticeable than in adults and can require more sophisticated techniques (e.g., EEG power spectrum analysis, Bandla & Gozal, 2000) for proper documentation. Along the same lines, we suggest that more detailed characterization of stimulus-related brain activity in children with SDB including examination of the ERPs preceding the oft-studies N2-P3 responses may offer additional insights about the presence and the mechanisms of injury in SDB and other sleep disorders.

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#### References

- American Thoracic Society. Standards and indications for cardiopulmonary sleep studies in children. American Journal of Respiratory Critical Care Medicine 1996;153:866–878.
- Archbold K, Giordani B, Ruzicka D, Chervin R. Cognitive executive dysfunction in children with mild sleep-disordered breathing. Biological Research for Nursing 2004;5:168–176. [PubMed: 14737917]
- Ayalon L, Peterson S. Functional central nervous system imaging in the investigation of obstructive sleep apnea. Current Opinion in Pulmonary Medicine 2007;13:479–483. [PubMed: 17901752]
- Ayalon L, Ancoli-Israel S, Aka AA, McKenna BS, Drummond SPA. Relationship between obstructive sleep apnea severity and brain activation during a sustained attention task. Sleep 2009;32:373–381. [PubMed: 19294957]
- Bandla HP, Gozal D. Dynamic changes to EEG during obstructive apnea in children. Pediatric Pulmonology 2000;29:359–365. [PubMed: 10790247]
- Bass J, Corwin M, Gozal D, Moore C, Nishida H, Parker S, Schonwald A, Wilker R, Stehle S, Kinane TB. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. Pediatrics 2004;114:805–816. [PubMed: 15342857]
- Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep 2006;29:1115–1134. [PubMed: 17040000]
- Beebe D, Gozal D. Obstructive sleep apnea and prefrontal cortex: Towards a comprehensive model linking nocturnal airway dysfunction to daytime cognitive and behavioral deficits. Journal of Sleep Research 2002;1:1–16. [PubMed: 11869421]
- Bloch-Salisbury E, Lansing R, Shea S. Acute changes in carbon dioxide levels alter the electroencephalogram without affecting cognitive function. Psychophysiology 2000;37:418–426. [PubMed: 10934900]
- Blunden S, Lushington K, Kennedy D. Cognitive and behavioral performance of children with sleeprelated obstructive breathing disorders. Sleep Medicine Reviews 2001;5(6):447–461. [PubMed: 12531153]
- Braun A, Balkin T, Wesensten N, et al. Regional cerebral blood flow throughout the sleep wake cycle. Brain 1997;20:1173–1197. [PubMed: 9236630]
- Breimhorst M, Falkenstein M, Marks A, Griefahn B. The relationship between poor sleep and inhibitory functions indicated by event-related potentials. Experimental Brain Research 2008;187:631–639.
- Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest 1995;108:610–618. [PubMed: 7656605]
- Carskadon M, Dement W. Acute restriction of nocturnal sleep in children. Perceptual and Motor Skills 1981;53:103–112.
- Carskadon M, Harvey K, Dement W. Sleep loss in young adolescents. Sleep 1981;4:299–312. [PubMed: 7302461]
- Chervin RD, Archbold KH. Hyperactivity and polysomnographic ndings in children evaluated for sleepdisordered breathing. Sleep 2001;24:313–320. [PubMed: 11322714]

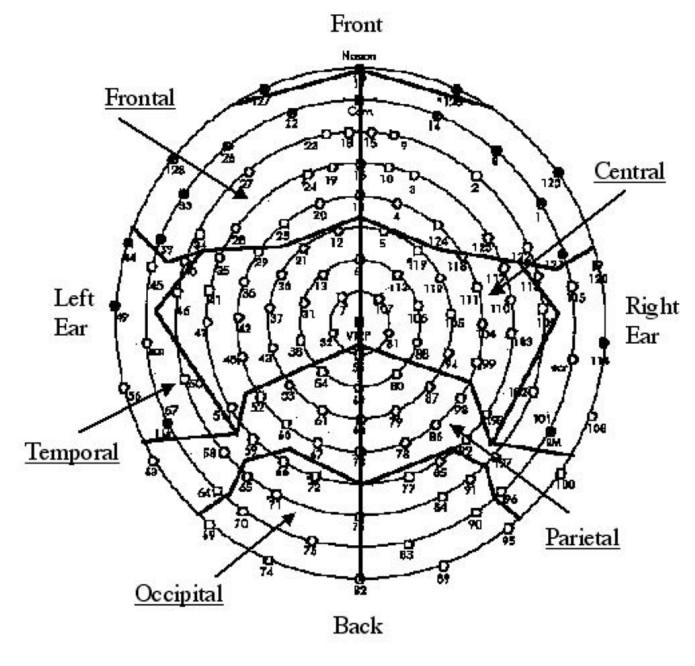
- Corsi-Cabrera M, Arce C, Del Rio-Portilla I, Perez-Garci E, Guevara M. Amplitude reduction in visual event-related potentials as a function of sleep deprivation. Sleep 1999;22:181–189. [PubMed: 10201062]
- Cote KA, Milner CE, Osip SL, Ray LB, Baxter KD. Waking quantitative electroencephalogram and auditory event-related potentials following experimentally induced sleep fragmentation. Sleep 2003;26(6):687–694. [PubMed: 14572121]
- Curran T. The electrophysiology of incidental and intentional retrieval: ERP old/new effect in lexical decision and recognition memory. Neuropsychologia 1999;37:771–785. [PubMed: 10408645]
- Cutting JE. Two left-hemisphere mechanisms in speech perception. Perception & Psychophysics 1974;16:601–612.
- Dahl R, Pelham W, Wierson M. The role of sleep disturbance in attention deficit disorder symptomatology: A case study. Journal of Pediatric Psychology 1991;16:229–239. [PubMed: 2061790]
- Dahl R. The impact of inadequate sleep on children's daytime cognitive function. Seminars in Pediatric Neurology 1996;3:44–50. [PubMed: 8795841]
- Thorpy, MJ, chair. Diagnostic Classification Steering Committee. International Classification of Sleep Disorders: Diagnostic and Coding Manual. Rochester, MN: American Sleep Disorders Association; 1990. Periodic limb movement disorder; p. 69-71.
- Dorsey C, et al. Spectroscopy before and after total sleep deprivation in healthy adult men. Sleep 2000;23 (Suppl 2):A357–A358.
- Goh DY, 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. [PubMed: 10934106]
- Gottlieb D, Chase C, Vezina R, Heeren T, Corwin M, Auerbach S, Weese-Mayer D, Lesko S. Sleepdisordered breathing symptoms are associated with poorer cognitive function in 5-year-old children. Journal of Pediatrics 2004;145:458–464. [PubMed: 15480367]
- Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998;102:616–620. [PubMed: 9738185]
- Gozal D, Pope D. Snoring during early childhood and academic performance at ages thirteen to fourteen years. Pediatrics 2001;107:1394–1399. [PubMed: 11389263]
- Gozal D, Wang M, Pope DW. Objective sleepiness measures in pediatric obstructive sleep apnea. Pediatrics 2001;108:693–697. [PubMed: 11533338]
- Guilleminault C, Winkle R, Korobkin R, et al. Children and nocturnal snoring: evaluation of the effects of sleep related respiratory resistive load and daytime functioning. European Journal of Pediatrics 1982;139:165–171. [PubMed: 7160405]
- Gregory A, O'Connor T. Sleep problems in childhood: A longitudinal study of developmental cange and associations with behavioral problems. Journal of the American academy of Child and Adolescent Psychiatry 2002;41(8):964–971. [PubMed: 12162632]
- Harrison Y, Horne J. Sleep deprivation affects speech. Sleep 1997;10:871–877. [PubMed: 9415947]
- Harrison Y, Horne J. Sleep loss impairs short and novel language tasks having a prefrontal focus. Journal of Sleep Research 1998;7:95–100. [PubMed: 9682180]
- Harrison Y, Horne JA. One night of sleep loss impairs innovative thinking and flexible decision making. Organizational Behavior & Human Decision Processes 1999;78:128–145. [PubMed: 10329298]
- Harrison Y, Horne J. Sleep loss and temporal memory. Quarterly Journal of Experimental Psychology 2000;53A:271–279. [PubMed: 10718074]
- Hill CM, Hogan AM, Onugha N, Harrison D, Cooper S, McGrigor VJ, Datta A, Kirkham FJ. Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: a possible association with abnormal neuropsychological function. Pediatrics 2006;118(4):e1100–1108. [PubMed: 17015501]
- Horne J. Sleep loss and "divergent" thinking ability. Sleep 1988;11:528-536. [PubMed: 3238256]
- Horne J. Human sleep, sleep loss and behaviour: implications for the prefrontal cortex and psychiatric disorder. British Journal of Psychiatry 1993;162:413–419. [PubMed: 8453439]
- Johnstone S, Tardif H, Barry R, Sands T. Nasal bilevel positive airway pressure therapy in children with a sleep-related breathing disorder and attention-deficit hyperactivity disorder: Effects on

electrophysiological measures of brain function. Sleep Medicine 2001;2:407–416. [PubMed: 14592390]

- Kennedy C, Meyer K. Sleep deprivation, allergy symptoms, and negatively reinforced problem behavior. Journal of Applied Behavioral Analysis 1996;29:133–135.
- Kennedy JD, Blunden S, Hirte C, et al. Reduced neurocognition in children who snore. Pediatric Pulmonology 2004;37:330–337. [PubMed: 15022130]
- Key AP, Molfese DL, Ratajczak ED. ERP indicators of learning in adults. Developmental Neuropsychology 2006;29(2):379–395. [PubMed: 16515411]
- Kingshott R, Cosway R, Deary I, Douglas N. The effect of sleep fragmentation on cognitive processing using computerized topographic brain mapping. Journal of Sleep Research 2000;9:353–357. [PubMed: 11386203]
- Korkman, M.; Kirk, U.; Kemp, S. NEPSY: a developmental neuropsychological assessment. San Antonio (TX): The Psychological Corporation; 1998.
- Lewin D, Rosen R, England S, Dahl R. Preliminary evidence of behavioral and cognitive sequelae of obstructive sleep apnea in children. Sleep Medicine 2002;3:5–13. [PubMed: 14592247]
- Luck SJ, Woodman GF, Vogel EK. Event-related potential studies of attention. Trends in Cognitive Science 2000;4:432–440.
- Marcus, CL.; Carroll, JL. Obstructive sleep apnea syndrome. In: Loughlin, GM.; Eigen, H., editors. Respiratory disease in children: diagnosis and management. Baltimore: Williams and Wilkins; 1993. p. 475-99.
- Mayes LC, Molfese DL, Key AP, Hunter NC. Event-related potentials in cocaine-exposed children during a Stroop task. Neurotoxicology and Teratology 2005;27:797–813. [PubMed: 16111858]
- Mindell JA, Owens JA, Carskadon MA. Developmental features of sleep. Child and Adolescent Psychiatry Clinics of North America 1999;8:695–725.
- Molfese D. Predicting dyslexia and 8 years of age using neonatal brain responses. Brain and Language 2000;72:238–245. [PubMed: 10764519]
- Molfese D, Molfese V. Electrophysiological indices of auditory discrimination in newborn infants: The bases for predicting later language development. Infant Behavior and Development 1985;8:197–211.
- Molfese D, Molfese V. Discrimination of language skills at five years of age using event-related potentials recorded at birth. Developmental Neuropsychology 1997;13(2):135–156.
- Molfese D, Molfese V, Kelly S. The use of brain electrophysiology techniques to study language: A basic guide for the beginning consumer of electrophysiology information. Learning Disabilities Quarterly 2001;24:177–188.
- Montgomery-Downs HE, O'Brien LM, Gulliver TE, Gozal D. Polysomnographic characteristics in normal preschool and early school-aged children. Pediatrics 2006;117(3):741–753. [PubMed: 16510654]
- National Sleep Foundation (NSF). 2004 Sleep in America Poll. Washington, DC: National Sleep Foundation; 2004.
- O'Brien LM, Holbrook CR, Mervis CB, Klaus CJ, Bruner J, Raffield TJ, Rutherford J, Mehl RC, Wang M, Tuell A, Hume BC, Gozal D. Sleep and neurobehavioral characteristics in 5-7-year-old hyperactive children. Pediatrics 2003;111:554–563. [PubMed: 12612236]
- O'Brien LM, Mervis CB, Holbrook CR, Bruner J, Smith N, McNally N, et al. Neurobehavioral implications of habitual snoring in children. Pediatrics 2004;114:44–49. [PubMed: 15231906]
- O'Brien LM, Tauman R, Gozal D. Sleep pressure correlates of cognitive and behavioral morbidity in snoring children. Sleep 2004;27:279–282. [PubMed: 15124723]
- Oldfield R. The assessment of handedness: The Edinburgh Inventory. Neuropsychologia 1971;9:97–113. [PubMed: 5146491]
- Owens J, Spirito A, Marcotte A, McGuinn M, Berkelhammer L. Neuropsychological and Behavioral Correlates of Obstructive Sleep Apnea Syndrome in Children: A Preliminary Study. Sleep Breath 2000;4(2):67–78. [PubMed: 11868122]
- Picchietti D, Walters A. Attention deficit hyperactivity disorder and periodic limb movement disorder. Sleep Research 1994;23:303.

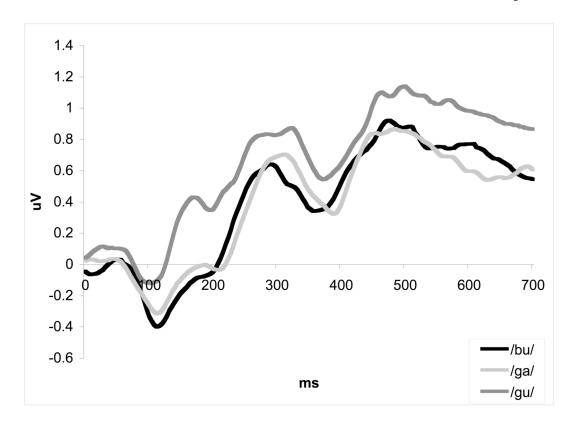
- Pilcher J, Huffcutt A. Effects of sleep deprivation on performance: A meta-analysis. Sleep 1996;19:318– 326. [PubMed: 8776790]
- Pressman M, Spielman A, Pollak C, Weitzman E. Long-latency auditory evoked responses during sleep deprivation and in narcolepsy. Sleep 1982;5:S147–S156. [PubMed: 7156649]
- Randazzo A, Muehlbach M, Schwitzer P, Walsh J. Cognitive function following acute sleep restriction in children ages 10–14. Sleep 1998;21:861–868. [PubMed: 9871948]
- Rechtschaffen, A.; Kales, A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subject. Washington DC: National Institutes of Health; 1968. Pul. No. 204
- Regestein Q, Dambrosia J, Hallett M, Murawski B, Paine M. Daytime alertness in patients with primary insomnia. American Journal of Psychiatry 1993;150:1529–1534. [PubMed: 8379559]
- Rumbach L, Krieger J, Kurtz D. Auditory event-related potentials in obstructive sleep apnea: effects of treatment with nasal continuous positive airway pressure. Electroencephalography and Clinical Neurophysiology 1991;80:454–457. [PubMed: 1716571]
- Sangal R, Sangal J. Abnormal visual P300 latency in obstructive sleep apnea does not change acutely upon treatment with CPAP. Sleep 1997;20:702–704. [PubMed: 9406320]
- Sleep Disorders Atlas Task Force. EEG arousals: scoring and rules and examples. In: Guilleminault, C., editor. Sleep. Vol. 15. 1992. p. 173-184.
- Steenari M-R, Vuontela V, Paavonen EJ, Carlson S, Fjallberg M, Aronen E. Working memory and sleep in 6- to 13-year-old school children. Journal of the American Academy of Child & Adolescent Psychiatry 2003;42(1):85–92. [PubMed: 12500080]
- Stickgold R. Toward a cognitive neuroscience of sleep. Sleep Medicine Review 2001;5:417-421.
- 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. [PubMed: 15124722]
- Thomas M, et al. Cerebral glucose utilization during task performance and sleep loss. Journal of Cerebral Blood Flow and Metabolism 1993;13(Suppl 1):S531.
- Thomas M, et al. PET imaging studies of sleep deprivation and sleep: Implications for behavior and sleep function. Journal of Sleep Research 1998;7(Suppl 2):274.
- Walsleben J, Squires N, Rothenberger V. Auditory event-related potentials and brain dysfunction in sleep apnea. Electroencephalography and Clinical Neurophysiology 1989;74:297–311. [PubMed: 2471631]
- Wimmer F, Hoffman R, Bonato R, Moffitt A. The effect of sleep deprivation on the divergent thinking and attention processes. Journal of Sleep Research 1992;1:223–230. [PubMed: 10607055]
- Wong KK, Grunstein RR, Bartlett DJ, Gordon E. Brain function in obstructive sleep apnea: results from the Brain Resource International Database. Journal of Integrative Neuroscience 2006;5(1):111–121. [PubMed: 16544369]

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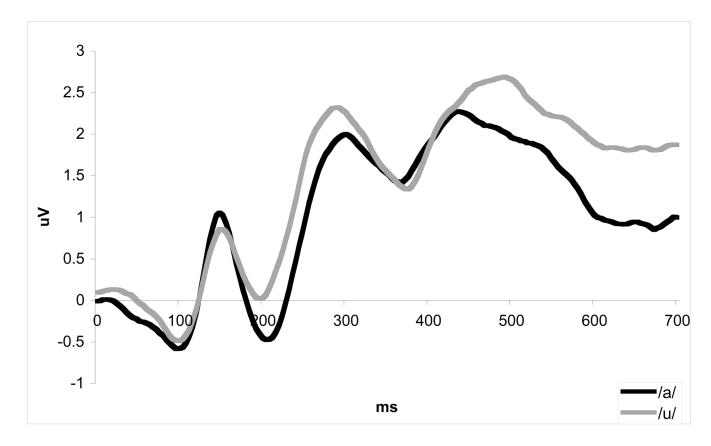
#### Figure 1.

Map of electrode distribution for the 128-channel Geodesic Sensor Net (EGI, Inc.) and the electrode clusters used for the analysis procedure in adult learning experiment. Midline electrodes (identified by the vertical line in the center of the plot) were excluded from the analysis.



#### Figure 2.

Grand-average ERP responses to syllables /bu/, /gu/, /ga/.



#### Figure 3.

Average ERPs responses to /a/- and /u/-ending syllables recorded at temporal scalp locations (averaged across hemispheres).

| characteristics.   |
|--|
| nmary of the participants' sleep and neurocognitive char |
| ts' sleep and  |
| he participant   |
| Summary of th  |

|    | Age       | Handedness (LQ) | Total apnea & hypopnea | Total apnea                       | Age Handedness (LQ) Total apnea & hypopnea Total apnea Apnea & hypopnea index | Apnea index             |
|----|-----------|-----------------|------------------------|-----------------------------------|---|-------------------------|
| Μ  | 6.54 yrs  | 0.44            | 11.34                  | 5.11                              | 1.51  | 0.7                     |
| SD | 6.43 mo   | 0.57            | 15.88                  | 4.27                              | 2.14  | 0.64                    |
|    |           |                 | Neurocognitiv          | Neurocognitive Assessment (NEPSY) | VEPSY)  |                         |
|    | Attn/Exec | Language        | Visuospatial           | Memory                            | Memory Speeded Naming (raw) Speeded Naming (scaled)                           | Speeded Naming (scaled) |
| Μ  | 103.18    | 101.21          | 99.44                  | 106.74                            | 13.62   | 60.6                    |
| SD | 15.29     | 17.73           | 12.37                  | 17.77                             | 8.4   | 3.67                    |