ORIGINAL ARTICLE

Heartbeat Evoked Potentials during Sleep and Daytime Behavior in Children with Sleep-disordered Breathing

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Abstract

Rationale: Event-related brain potentials allow probing of cortical information processing, but when evoked with externally induced stimuli may disrupt sleep homeostasis and do not provide insight into intrinsic cortical information processing. To investigate if cortical processing of intrinsic information in children with sleep-disordered breathing (SDB) is different from healthy children and, if so, whether it resolves with treatment, we used heartbeat as a source of interoceptive event-related brain potentials.

Objectives: To investigate heartbeat evoked potentials (HEP) during sleep in healthy children and in children with SDB before and after treatment and to explore if there are any associations between HEP and daytime behavioral deficits in children with SDB.

Methods: Heartbeat-aligned EEG was assessed for presence of HEP within stage 2, slow-wave sleep, and REM sleep in 40 children with primarily mild to moderate SDB before and after adenotonsillectomy and in 40 matched control subjects at similar time points.

Measurements and Main Results: In both groups, nonrandom HEP were present in all sleep stages analyzed; however, amplitude of HEP were significantly lower in children with SDB during non-REM sleep (stage 2: $P = 0.03$; slow-wave sleep: $P = 0.001$). This between-group difference was not significant post adenotonsillectomy. Significant negative associations between HEP and daytime behavioral scores were observed at baseline.

Conclusions: Children with SDB displayed reduced HEP amplitude during sleep, which might be indicative of changes in afferent sensory inputs to the brain and/or signify differences in sensory gating of cardiac-related information in the insular cortex. Adenotonsillectomy appears to reverse this effect.

Keywords: cardiac cycle; heartbeat evoked potential; adenotonsillectomy; behavior; children

Event-related brain potentials (ERP) to sensory stimuli have been studied in healthy adults and children (1, 2) during wakefulness and sleep (3). They are influenced by the amount of neuronal activity reaching the cortex and the level of vigilance during sleep/wake states (4, 5). In children with obstructive sleep apnea syndrome (OSAS), respiratory ERP elicited via upper airway occlusions are attenuated, suggesting impaired afferent cortical processing of respiratory stimuli (6, 7). To date, ERP studies during sleep have focused on cortical responses to externally induced auditory and respiratory stimuli, which may disrupt sleep homeostasis and do not elucidate information on visceral information processing. We therefore used heartbeat as a source of intrinsic ERP. Heartbeat evoked potentials (HEP) were first described by Schandry and colleagues

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At a Glance Commentary

Scientific Knowledge on the Subject: During sleep, children with sleep-disordered breathing (SDB) exhibit normal cortical processing of auditory stimuli, but respiratory cortical processing is impaired. It is unknown whether cortical processing of visceral information during sleep is altered as well and, if so, whether it resolves with treatment.

What This Study Adds to the Field: This study is the first demonstration of cortical processing of visceral stimuli, evoked by the heartbeat during sleep. Importantly, heartbeat evoked potentials were attenuated in children with primarily mild to moderate SDB, indicating increased sensory gating of cardiac information via afferent inputs reaching the cortex; adenotonsillectomy appears to reverse this effect.

(8) and are used as a psychophysiological indicator of interoceptive cortical processing (9, 10). Research suggests two different pathways mediate these HEP: the cyclical mechanical impact of the heart on the chest wall resulting in neuronal signals via somatosensory pathways (11) and via visceral cardiac afferents to the frontal cortical areas (12, 13). With the afferent cardiac pathway being primarily responsible for the perception of cardiac symptoms (14) and studies demonstrating correlation between HEP and interoception, it has been argued that HEP provide an indirect measure of afferent signals arriving at the cortex that are crucial for cardiac control (15).

Attention and cardiac awareness are reflected in the amplitude of HEP and, in psychopathological conditions where interoceptive awareness is reduced, such as depression, the HEP is reduced (16). Because there is substantial evidence for cognitive and behavioral deficits (17, 18) and an increased risk of developing cardiovascular morbidities in children with sleep-disordered breathing (SDB) (19, 20), impaired cardiac interoception may be an important key in the cardiovascular sequela seen in SDB. We therefore measured HEP during sleep in children with SDB to identify potential differences from normal children using overnight polysomnograms (PSG). We studied sleep periods free of scored apnea/hypopneas, arousals, or artifacts during the entire night to test (*1*) whether HEP exist during sleep, (*2*) whether HEP differ between sleep stage, (*3*) if the magnitude and time latency of HEP in children with SDB differ significantly from healthy children, and (*4*) if so, whether the difference is still present after the children with SDB underwent adenotonsillectomy. Furthermore, we sought to explore the relationship between HEP and daytime behavior.

Methods

Subjects and Overnight Polysomnography

This study was approved by the Women's and Children's Health Network Human Research Ethics Committee, South Australia, with parental consent and child assent obtained from all participants. Participants were 40 children aged 3 to 13 years, with a history of frequent snoring, awaiting adenotonsillectomy for suspected SDB and a matched group of 40 nonsnoring healthy control subjects. Children with SDB had two PSGs, one before and one after surgical intervention (adenotonsillectomy), and control children had two PSGs at the same time points. For details on the PSG methodology, *see* the online supplement. A repeat study was

Table 1. Subject Demographic, Sleep, and Respiratory Parameters at Baseline and Follow-up Study

	Baseline		Follow-up	
	Control (*n* = *40*)	SDB (*n* = *40*)	Control (*n* = *36*)	SDB (*n* = *32*)
Age, yr	7.5 ± 2.6	7.5 ± 2.7	8.2 ± 2.6	7.8 ± 2.6
Sex, male, n (%)	20 (50)	24 (60)	19 (52.7)	20 (62.5)
BMI, percentile (%)	60.7 ± 26.4	65.8 ± 31.9	61.5 ± 25.9	71.7 ± 29.2
TST, min	446.9 ± 37.3	425.6 ± 59.5	451.5 ± 50.5	437.3 ± 53.9
Stage 2 sleep, % TST	44.2 ± 6.9	42.4 ± 6.2	47.6 ± 4.8	42.2 ± 7.4*
SWS, % TST	32.2 ± 6.3	34.4 ± 6.5	30.0 ± 5.0	33.7 ± 6.2†
REM sleep, % TST	20.6 ± 3.9	19.7 ± 5.7	19.5 ± 3.5	20.6 ± 3.3
SAI	9.4 ± 2.7	8.4 ± 2.4	9.2 ± 2.7	9.4 ± 2.9
RAI,‡ mean ± SD (median, range)	0.4 ± 0.4 (0.3, 0–1.7)	3.2 ± 4.2§ (1.1, 0–17.0)	0.5 ± 0.5 (0.4, 0–2.4)	0.8 ± 0.7 (0.6, 0–2.6)
Sp_{O_2} nadir, %	92.9 ± 1.9	90.6 ± 5.7‖	93.1 ± 1.6	91.0 ± 3.1*
Sp_{O_2} desaturation index,‡ mean ± SD (median, range)	0.8 ± 0.8 (0.8, 0–4.9)	5.1 ± 9.4§ (1.3, 0–53.1)	0.8 ± 0.7 (0.6, 0–3.0)	1.5 ± 0.9* (1.0, 0–3.1)
OAHI,‡ mean ± SD (median, range)	0.1 ± 0.2 (0.1, 0–0.9)	5.0 ± 9.0§ (0.9, 0–49.8)	0.3 ± 0.3 (<0.1, 0–0.5)	1.0 ± 0.2‖ (0.2, 0–3.2)

Definition of abbreviations: BMI = body mass index; OAHI = obstructive apnea-hypopnea index; RAI = respiratory arousal index; SAI = spontaneous arousal index; SDB = sleep-disordered breathing; SWS = slow-wave sleep; TST = total sleep time.
Data are presented as mean ± SD unless otherwise indicated.
*$P < 0.005$.
†$P < 0.01$.
‡Analysis using transformed values.
§$P < 0.001$.
‖$P < 0.05$.

performed on average 28.0 ± 5.0 weeks later in control subjects and 32.4 ± 6.7 weeks later in children with SDB. An experienced sleep technician blinded to child status scored sleep stages using standardized criteria (22). Respiratory events were scored using pediatric criteria. For details of scoring, *see* the online supplement. During both studies, parents of participants were asked to complete the Child Behavior Checklist (21), a standardized questionnaire for assessment of child internalizing and externalizing behavior, which is available in two versions, for children aged 6 to 18 years and for children aged 1.5 to 5 years, with equivalent domains. Subdomain scores available across the full age range of participating children included those of anxious and depressed symptoms, withdrawal, somatic complaints, attention problems, and aggressive behavior. Scores at which clinically significant symptoms are determined on the Child Behavior Checklist are defined as a *t* score greater than or equal to 70.

Data Analysis

EEG data from the central electrode with best signal quality were extracted from PSG and analyzed using custom written algorithms developed in MATLAB (*see* online supplement). Stage 2 non-REM (NREM), slow-wave sleep (SWS; stages 3 and 4), and REM sleep were considered. Data segments of artifact-free uninterrupted sleep (Scored Event Free periods [SEF]) were retained, and all portions of data falling within durations scored as body movements or abnormal cardiorespiratory events were excluded. Within each sleep stage, the EEG and ECG during retained SEF 30-second epochs were extracted and used for analysis. Also, the RR intervals of cardiac cycles used in our analysis were extracted and compared between the groups.

Extraction of HEPs

In SEF periods, EEG from within each RR interval was extracted over the entire night and R-peak-aligned average curves computed within sleep stages 2, SWS, and REM. Although brain activity generates an electric current that is localized to the scalp, the heart's electrical activity can be measured anywhere on the body surface and is therefore included in EEG recordings along with brain electric components (12). This inherent artifact, termed cardiac field artifact (CFA), is most prominent during ventricular depolarization (QRS complex), and its influence is considered negligible in the post-repolarization (T-wave) interval (24). Thus, we considered each subject's average EEG curve between 400 and 550 milliseconds post R-peak, representing a "low CFA window" (*see* the online supplement for details). The low-CFA window was divided into 10 15-millisecond segments, and the mean EEG amplitude was calculated from within each segment. Furthermore, the maximum positive deflection of each child's average EEG curve within the low-CFA window was identified (HEP peak in μV), and the corresponding time latency from the R-peak was measured (HEP latency in milliseconds).

Surrogate Analysis

To test whether the heartbeat-related average EEG curves represent HEP and are different from spurious random fluctuations in EEG, we performed surrogate analysis using EEG and ECG data from the control group at baseline study. The surrogate data were obtained by shuffling the order of RR intervals and constructing a new R-peak time series, by stepwise adding subsequent RR intervals. The cumulated time at each added RR interval was used to denote the randomized R-peak. The averaged EEG curves from these randomized RR intervals were extracted and analyzed with respect to sleep stage as described above.

Statistical Analysis

Data were analyzed using the Prism (GraphPad Software, Inc.) version 5.01 for Windows. Normality of data distribution was tested using the Kolmogorov-Smirnov tests. Student *t* test and one-way analysis of variance (ANOVA) were used to compare demographic, behavior data and PSG results between groups. A two-way repeated measures ANOVA between the amplitude of the EEG segments was used to test for differences in HEP between (*1*) real and surrogate data, (*2*) sleep stages within each group, (*3*) control and SDB group at baseline, (*4*) control and SDB group at follow-up study. To test for within-group sleep stage–specific time effects in HEP amplitude between the segments, one-way repeated measures ANOVA was used. The HEP peak and latencies were tested for group effect and sleep stage effect using two-way ANOVA. *Post hoc* comparison between groups within each sleep stage was done using Student *t* test, and comparison between sleep stages within each group was done using one-way ANOVA. To test for the effect of surgery, two-way ANOVA of

Table 2. Subject Behavior Ratings at Baseline and Follow-up Study

	Baseline		Follow-up	
	Control	SDB	Control	SDB
Total problems	49.5 ± 10.2	58.8 ± 11.7*	46.0 ± 9.7	55.4 ± 12.7*
Internalizing problems	48.5 ± 10.4	59.8 ± 12.4†	46.9 ± 9.5	55.3 ± 12.4*
Externalizing problems	49.6 ± 10.7	55.4 ± 12.7‡	47.3 ± 9.7	55.6 ± 11.9*
Syndrome scales				
Anxious	53.2 ± 5.2	59.6 ± 10.4*	52.0 ± 4.1	56.7 ± 7.5§
Withdrawn	53.4 ± 5.1	58.1 ± 7.2*	52.3 ± 3.8	55.8 ± 7.1‡
Somatic complaints	54.9 ± 6.3	61.8 ± 11.0*	55.1 ± 6.9	59.6 ± 9.5‡
Attention problems	55.3 ± 8.5	58.2 ± 8.9	53.9 ± 5.8	57.6 ± 9.7
Aggressive	54.1 ± 6.2	58.8 ± 10.8‡	51.2 ± 8.7	58.7 ± 10.0§
DSM-oriented scales				
Affective problems	54.6 ± 5.9	58.2 ± 8.9*	52.5 ± 4.4	58.2 ± 8.4†
Anxiety problems	53.0 ± 5.5	58.6 ± 9.4*	52.0 ± 4.1	56.7 ± 7.5*
ADHD Problems	54.5 ± 6.3	56.8 ± 7.2	52.9 ± 5.4	56.3 ± 7.8
Oppositional/defiant	54.8 ± 6.5	58.4 ± 8.4‡	52.9 ± 4.0	57.1 ± 8.0‡

Definition of abbreviations: ADHD = attention deficit hyperactivity disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders; SDB = sleep-disordered breathing.
Data shown are *t* scores for the CBCL scales and are presented as mean ± SD.
*$P < 0.005$.
†$P < 0.001$.
‡$P < 0.05$.
§$P < 0.01$.

HEP peaks with group and baseline versus follow-up as the two factors was performed. Associations between HEP peaks and age, body mass index, obstructive apnea-hypopnea index (OAHI), and behavior indices were determined using Pearson or Spearman correlation coefficients with bootstrapping, as appropriate. All data were normally distributed, and P values with $P < 0.05$ were considered statistically significant.

Results

Subject Characteristics and PSG Results

Results of overnight PSG have been reported earlier (25, 26). Baseline PSG confirmed the presence of respiratory abnormalities in children with SDB, who had a significantly higher OAHI, elevated frequency of respiratory arousals, increased frequency of oxygen saturation as measured by pulse oximetry (Sp_{O_2}) desaturations, and a significantly lower mean Sp_{O_2} nadir compared with control subjects. Overall, the degree of SDB can be considered mild to moderate (OAHI, 5.0 ± 9.0). At baseline, 20 children with SDB (50%) had an OAHI greater than 1.0, indicative of OSAS, and the remaining were classified as primary snorers. Sleep architecture in the baseline PSG was comparable between groups, whereas small differences were observed during follow-up (Table 1). After adenotonsillectomy, there was a marked reduction in OAHI, Sp_{O_2} desaturation frequency, and respiratory arousal rate in children with SDB, but they still had a small but significantly higher OAHI and Sp_{O_2} desaturation frequency and lower Sp_{O_2} nadir. Increased symptoms of withdrawal, somatic complaints, aggressive behavior, anxiety, and depression and elevated affective disorder, anxiety disorder, and oppositional defiant symptoms were seen in the SDB group (Table 2). Overall, both internalizing and externalizing problematic behavior was pronounced in children with SDB, and all significant differences at baseline were still evident at follow-up. The control group showed a small reduction in most scores during follow-up, which may be attributed to maturation.

Characterization of HEP

Heartbeat-related averaged EEG showed distinct characteristic features in all three

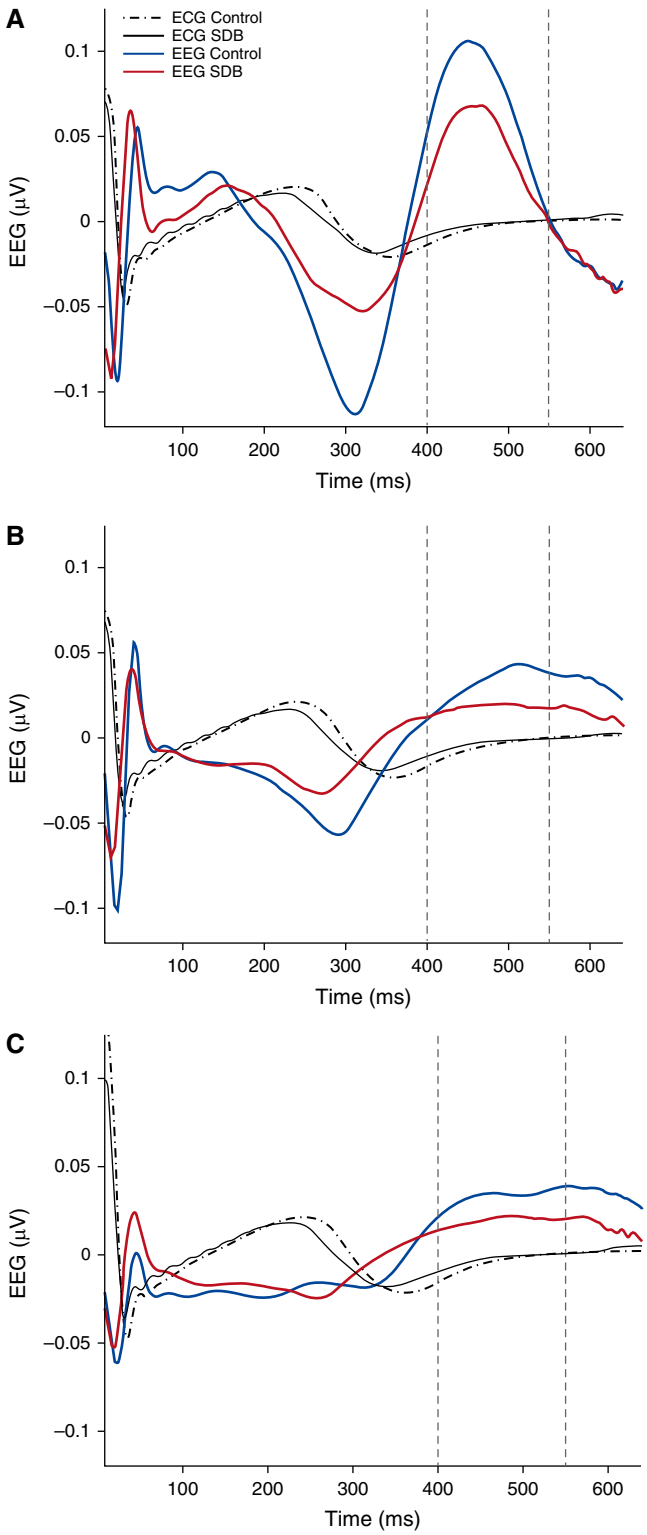

Figure 1. Ensemble average of R-peak-aligned EEG in normal children and in children with sleep-disordered breathing (SDB) during REM sleep (*A*), stage 2 non-REM (*B*), and slow-wave sleep (*C*) at baseline study. Children with SDB showed attenuated heartbeat-related evoked potentials at baseline compared with control subjects in all three sleep stages. The R-peak-aligned ECG average curves of the control and SDB group, both scaled down by 40 times, are shown in the background. The *dashed vertical lines* indicate the low cardiac field artifact window (i.e., 400–550 ms after R-peak).

sleep stages: a sharp early biphasic potential at the time of the QRS complex in ECG (within 100 milliseconds from R-peak), reflecting the CFA; a negative deflection with the onset at around 200 milliseconds; and a positive deflection with an onset at around 350 to 380 milliseconds after R-peak (Figure 1). In REM sleep, a distinct positive deflection at around 120 milliseconds was also observed. Negative and positive deflections were most pronounced during REM sleep and decreased in amplitude during stage 2 and were further attenuated during SWS. Average EEG curves of all participants within each group and sleep stage are presented in the online supplement (*see* Figure E1 in the online supplement). Because the negative deflections in all stages and the early positive deflection in REM sleep occurred during the ventricular repolarization phase and thus may contain CFA, quantitative analysis was restricted to the late positive deflection, which was within the low-CFA window. Between the groups, sleep stage–specific mean RR interval and overall RR interval variability were not statistically different (Table 3), and hence the quantitative HEP analysis was performed between similar time points (400–550 milliseconds post R-peak) in both groups.

Surrogate Data Analysis

At baseline study in control subjects, segmental EEG amplitudes computed from within the low-CFA window of real EEG data were significantly higher than those computed from corresponding RR interval–randomized EEG surrogates in all three sleep stages (stage 2: $P < 0.0001$; SWS: $P < 0.0001$; REM: $P = 0.001$), demonstrating the existence of HEP during sleep (Figure 2).

Mean EEG Amplitudes within the Low-CFA Window in Control Subjects and Children with SDB

Comparing the low-CFA segmental EEG amplitudes between control subjects and children with SDB at baseline, a significant group effect was observed in stage 2 ($P < 0.0001$), SWS ($P < 0.0001$), and REM sleep ($P = 0.0001$) with the EEG amplitude being lower in the SDB group (Figure 2). Time and group-by-time interaction effects were significant in stage 2 and REM sleep ($P < 0.0001$). *Post hoc* analysis showed a significant time effect in segmental EEG amplitudes during stage 2 in the control group ($P < 0.0001$) and during REM sleep in both groups (control: $P < 0.0001$; SDB: $P = 0.002$). Comparing segmental EEG amplitudes obtained from children with SDB post adenotonsillectomy to the repeat study of control subjects, the group differences observed at the baseline study were no longer significant, but time and interaction effects remained.

Peak Amplitudes and Time Latencies of HEP in Control Subjects and in Children with SDB

At baseline, a significant group effect ($P = 0.002$) and sleep stage effect ($P < 0.0001$) but no interaction effect was observed for HEP peaks. *Post hoc* between-group comparison showed that HEP peaks were significantly lower in children with SDB in stage 2 sleep ($P = 0.03$) and SWS ($P = 0.001$). In REM sleep, HEP peaks were lower in the SDB group, but the difference did not reach statistical significance (0.114 ± 0.085 vs. 0.138 ± 0.065, $P = 0.2$). *Post hoc* within-group comparison showed significantly higher HEP peaks during REM sleep than in stage 2 and SWS ($P < 0.0001$). HEP latencies were similar between the two groups and showed significant sleep stage differences within the control group ($P = 0.0004$). *Post hoc* analysis showed significantly longer HEP latencies during stage 2 sleep than during REM sleep ($P = 0.0002$).

Post adenotonsillectomy, HEP peaks in the SDB group were no longer significantly different from control subjects, whereas the sleep stage effect remained ($P < 0.0001$), with HEP peaks during REM sleep higher than those of stage 2 and SWS. Significant interaction effects between baseline and follow-up were observed in HEP peaks during stage 2 NREM sleep ($P = 0.03$) and SWS ($P = 0.008$) (Figure 3). HEP latencies at follow-up study in control subjects confirmed the significant sleep stage effect observed at baseline, with latencies during stage 2 longer than REM sleep ($P = 0.02$).

Clinical Correlates of HEP

The HEP peaks did not show any significant correlations with age, body mass index, or OAHI in either of the groups. At baseline, HEP peaks and behavior domain and subdomain scores showed mild negative

Table 3. Heartbeat-related Evoked Potentials during Stage 2 Non-REM, Slow-Wave Sleep, and REM in Children with Sleep-disordered Breathing and Control Subjects at Baseline and Follow-up Study

		Baseline			Follow-up		
		Control	SDB	*P* Value	Control	SDB	*P* Value
Stage 2	HEP peak, μV	0.059 ± 0.031	0.045 ± 0.027	0.03	0.052 ± 0.02	0.057 ± 0.025	0.1
	Latency, ms	496 ± 44	480 ± 50	0.1	485 ± 52	476 ± 54	0.5
	Mean RR, ms	794 ± 97	763 ± 105	0.1	815 ± 102	808 ± 119	0.7
	SD RR, ms	80.5 ± 31.0	82.2 ± 40.8	0.8	78.6 ± 29.0	85.7 ± 34.8	0.3
SWS	HEP peak, μV	0.057 ± 0.031	0.033 ± 0.026	0.001	0.046 ± 0.03	0.053 ± 0.035	0.9
	Latency, ms	475 ± 53	476 ± 57	0.9	484 ± 56	476 ± 55	0.6
	Mean RR, ms	782 ± 107	756 ± 90	0.2	798 ± 107	791 ± 120	0.8
	SD RR, ms	68.3 ± 31.7	70.0 ± 36.7	0.8	65.5 ± 29.4	69.4 ± 35.6	0.6
REM	HEP peak, μV	0.138 ± 0.065	0.114 ± 0.085	0.2	0.128 ± 0.08	0.116 ± 0.081	0.5
	Latency, ms	453 ± 33	459 ± 44	0.5	453 ± 31	444 ± 28	0.07
	Mean RR, ms	745 ± 97	730 ± 88	0.4	780 ± 87	753 ± 99	0.2
	SD RR, ms	71.5 ± 31.3	71.8 ± 34.5	0.9	83.3 ± 35.6	82.2 ± 38.8	0.9

Definition of abbreviations: HEP = heartbeat-related evoked potential; RR = RR interval; SDB = sleep-disordered breathing; SWS = slow-wave sleep. Data are presented as mean ± SD.

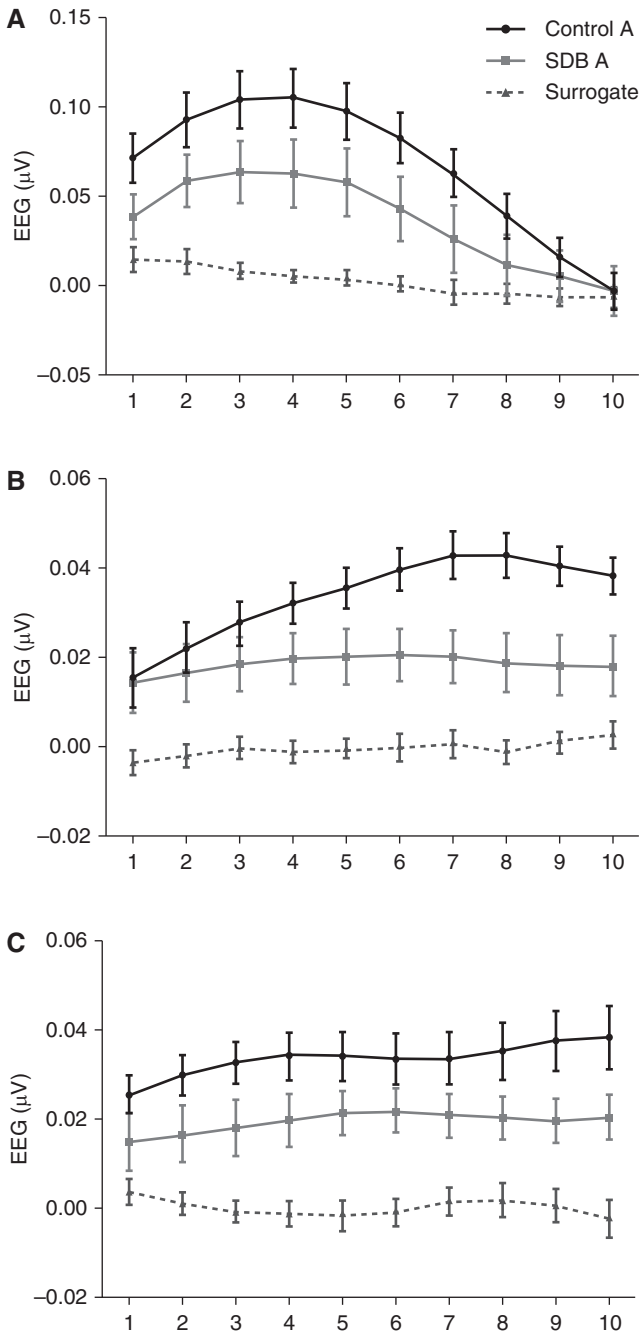

Figure 2. Mean EEG amplitude within the low-cardiac field artifact window of 150 milliseconds (grouped into 10 15-millisecond segments) in children with sleep-disordered breathing (SDB) compared with normal children during REM sleep (*A*), stage 2 non-REM (NREM) (*B*), and slow-wave sleep (SWS) (*C*) at baseline study. Segmental EEG amplitudes were significantly lower in the SDB group than in control subjects during stage 2 NREM and SWS. Segmental EEG amplitudes derived from surrogate data of control subjects, which were significantly different from their real data in all three sleep stages, are also shown. *Error bars* indicate SEM.

associations with overall internalizing behavior ($r = -0.27$, $P = 0.03$) in stage 2 NREM sleep; with anxious/depressed behavior ($r = -0.32$, $P = 0.01$), withdrawn behavior ($r = -0.31$, $P = 0.01$), symptoms of affective disorder ($r = -0.25$, $P = 0.03$), symptoms of anxiety disorder ($r = -0.3$, $P = 0.01$), and overall internalizing behavior ($r = -0.28$, $P = 0.02$) in SWS (Figure E2 in the online supplement); and with symptoms of attention disorder ($r = -0.28$, $P = 0.02$) and oppositional defiant disorder ($r = -0.27$, $P = 0.03$) in REM sleep. All significant associations indicated increasing problematic behavior with reductions in HEP peak amplitude. No significant associations between HEP peak and behavior were found at follow-up.

Discussion

The main findings of our study were: (*1*) the existence of sleep stage–specific, nonrandom biphasic HEP in the EEG of control subjects and those with SDB; (*2*) significantly reduced HEP amplitude during NREM sleep in the SDB group compared with healthy control subjects; (*3*) inverse correlations between HEP amplitude and behavioral scores; and (*4*) normalization of HEP amplitude in children with SDB post adenotonsillectomy.

By performing surrogate analyses with randomly shuffled R-peak locations we were able to demonstrate nonrandom biphasic HEP in the central cortical region throughout NREM and REM sleep in children. The HEP were relatively sharp and pronounced in REM sleep, with average amplitude of 0.1 μV on the negative and positive peaks. During stage 2, the biphasic HEP were broader than during REM sleep, whereas their maximum positive and negative amplitudes were around one-half of those observed during REM sleep. SWS showed significant positive HEP deflections, but with even smaller amplitudes than stage 2. HEP in the low-CFA interval were prominent in all three sleep stages, with a positive mean activity starting from around 380 milliseconds after R-peak and lasting around 200 milliseconds. The latencies of the positive HEP peaks ranged between 440 and 520 milliseconds, with NREM exhibiting higher latencies than REM sleep. The gradual attenuation of HEP from REM sleep to SWS is likely a reflection of the differences in level of cortical activation and suggests sleep-related differences in viscero-afferent neurotransmission. Previous studies have shown sleep stage differences in extrinsic ERPs evoked with auditory, respiratory, and somatosensory stimuli (3), where REM sleep responses were closer to those in wakefulness and distinctly different from responses during NREM sleep (27).

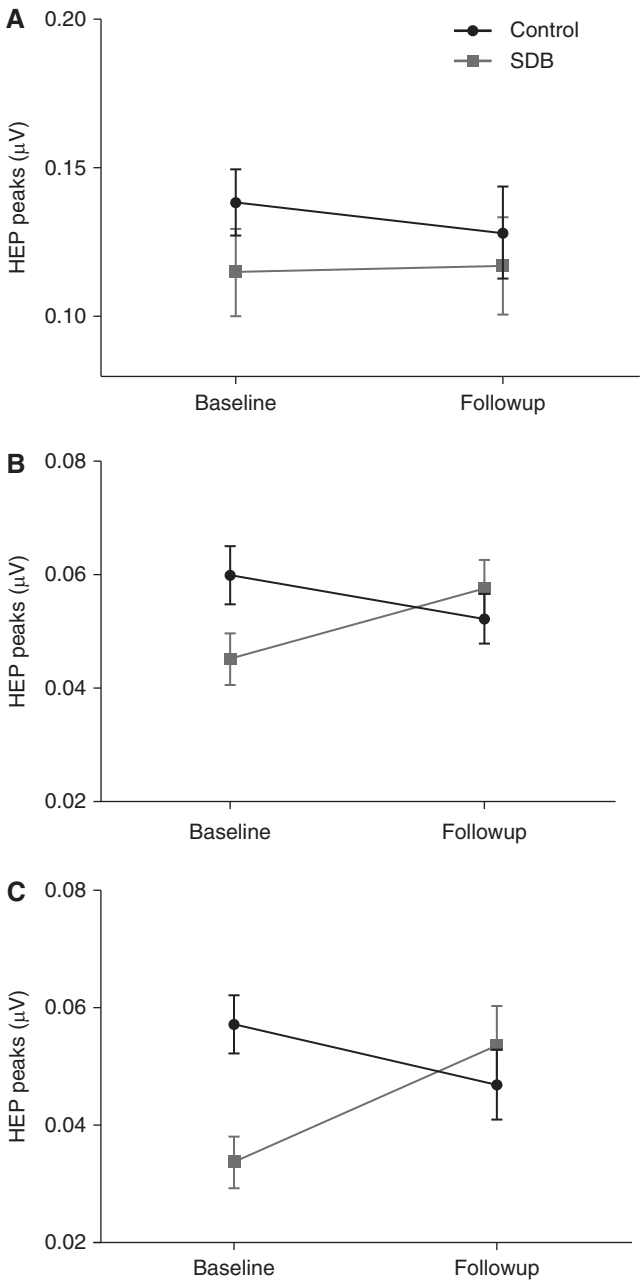

Figure 3. Comparison of peak amplitudes of heartbeat-evoked potentials between baseline and follow-up studies in normal children and in children with sleep-disordered breathing (SDB) during REM sleep (*A*), stage 2 non-REM (NREM) (*B*), and slow-wave sleep (SWS) (*C*). Significant interaction effects between baseline and follow-up studies were observed in stage 2 NREM and SWS. *Error bars* indicate SEM.

The neural mechanisms that lead to HEP have not been fully elucidated. The morphology and latency of HEP were found to vary with the location of electrodes on the scalp surface (10, 28). Most studies that have reported HEP in frontal and central scalp regions argue for the transmission of heartbeat-related evoked components via visceral pathways to the insular cortex (8, 10, 28), and in one of these studies insular origin of HEP was indirectly confirmed (29). These findings agree with the established role of insula as the primary cortical site for cardiac interoception (30, 31). Brain imaging studies consistently reported insula activation during general cardiovascular arousal (32, 33) and during angina provocation in cardiac patients (34). However, an alternative hypothesis relating HEP to somatosensory pathways that lead to parietal regions has also been presented (23). Attenuated cortical activation as evidenced by reduced EEG amplitude of evoked responses may signify disruption to white or gray matter function (35).

In our study, the amplitude of HEP was smaller in children with SDB than in control subjects. Although speculative, this may be due to alterations in cardio-afferent processing or abnormalities in cerebral structure or function. Cardiovascular and autonomic dysfunction has been found in children with OSAS (36, 37). In patients with autonomic diabetic neuropathy, where afferent pathways innervating the heart are impaired, HEP amplitude was significantly reduced, with the degree of attenuation correlating with severity of autonomic symptoms (9). Auditory ERP elicited in children with SDB during wakefulness exhibited altered patterns compared with control subjects (43), which were associated with their sleep-related respiratory disturbance index (38). However, during sleep, cortical processing of auditory ERP were found to be unaffected in children with OSAS (7), but their afferent processing of respiratory stimuli has been found to be different from control subjects, with the largest differences observed in SWS (6, 7). In line with this, HEP in our SDB group were lower than control subjects in all three sleep stages analyzed, but the difference was pronounced in NREM and did not reach statistical significance during REM. This might suggest that interoceptive processing deficits may occur primarily during NREM sleep. In our study, the latency of HEP peaks was similar between normal subjects and children with SDB. In adult patients with OSAS, normal latencies of respiratory ERP (39), but prolonged latencies of auditory and visual ERP have been reported previously (40, 41). This apparent discrepancy might be attributed to differences in the cortical processing of intrinsic and extrinsic information, where auditory and visual stimuli involve cognitive stimulus categorization.

Our data also suggest an association between HEP and problematic daytime behavior, which is a common clinical finding in children with SDB (42). Although individual correlations were small, the consistent pattern across different behavior scores makes solely random effects implausible. Sleep fragmentation

and/or hypoxia may cause neuronal damage, and cerebral abnormalities have been demonstrated in children with OSAS, particularly in the hippocampus and frontal cortex, areas that mediate learning and behavior (44–46). Thus, the correlations observed in this study between HEP and problematic behaviors may be an indirect marker of neuronal impairment. Auditory ERP elicited during wakefulness in children with OSAS were associated with neurobehavioral measures (43). Altered cardiac awareness has been repeatedly demonstrated in psychopathological conditions such as depression (16, 47), anxiety, and panic disorders (48), and the brain areas involved in the representation of visceral responses have been elucidated (33). It has been previously shown that upper airway obstruction in children with SDB alters cardiovascular control (49). An earlier study on the same dataset demonstrated an augmented heart rate increase associated with spontaneous cortical arousals in children with SDB compared with control subjects, indicating early autonomic dysfunction (50), whereas mean RR interval and overall RR variability were normal. Gray and colleagues have reported correlations between HEP and cardiac variables such as myocardial repolarization and cardiac output, suggesting that HEP serves as a cortically recorded index of cardiac function (15). Thus, one might speculate that reduced HEP in the children with SDB may be linked to future cardiovascular morbidity in addition to impaired cortical processing. In view of the available literature, our data suggest that attenuated cardiac interoception is just one aspect of a more general impaired cortical processing in children with SDB, even with mild to moderate severity levels. A comprehensive study of brain function using ERP and functional magnetic resonance imaging techniques is needed to obtain a more complete understanding of how brain function is affected in children with SDB.

Importantly, our data suggest that dampened cardiac interoception is reversible in children with mild to moderate SDB because attenuated HEP during NREM sleep were no longer present after adenotonsillectomy. In contrast, problematic behavior in the SDB group remained elevated relative to control subjects post treatment. One possible explanation is that learned behavior will take longer to "unlearn" after correcting the pathophysiological mechanisms of SDB that may have initially predisposed children to develop it in the first place. A longer-term follow-up of these children will help to clarify such a possibility.

Our study has several limitations. Sex effects of HEP during sleep cannot be ruled out but were beyond the scope of this study. We were not able to quantify the early part of the HEP due to the CFA and the lack of multilead EEG and ECG, which may have allowed its isolation, using independent component analysis. Although qualitative analysis suggests characteristics very similar to that of the positive deflection with respect to sleep stage and pathology, important information might have been ignored. The frequency response of the human body might cause a delay in the propagation of cardiac electrical activity from heart to the scalp that lead to a phase shift in CFA. However, the HEP amplitude with respect to the QRS induced CFA amplitude, together with he insignificant time delay between QRS complex in ECG and the corresponding CFA in EEG, do not suggest a significant effect of the CFA beyond the T wave.

In conclusion, we have demonstrated for the first time the existence of HEP during sleep. Children with primarily mild to moderate SDB showed attenuated HEP during NREM sleep, which correlated with deficits in daytime behavior. Importantly, HEP normalized after adenotonsillectomy, suggesting beneficial effects of adenotonsillectomy for brain function. HEP analysis may therefore have a role in the clinical assessment of sleep disorders and cortical function. It provides a simple tool to study interoceptive information processing during sleep and can be easily measured in the sleep laboratory using standard PSG. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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